CLINICAL USE OF DRUG BLOOD LEVELS

Internal Medicine Grand Rounds

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INTRODUCTION

The exercise of optimal therapeutics requires matching the dose of the drug one administers to the response manifest in the individual patient. With many drugs, this task is simple, particularly if there is a great difference between the amount of drug causing efficacy and that causing toxicity. In such cases we can often dose with relative impunity and take the therapeutic strategy of "overkill" to insure that efficacious amounts of drug are administered. Unfortunately, with many drugs, we have this latitude, and only a narrow margin exists between efficacy and toxicity. To make matters worse, for many of the drugs which fall into this category, lack of salutory effects has serious consequences, for the diseases with which one is dealing are severe and, on the other hand, the toxicities of these drugs are also severe and can be life-threatening. Consequently, we are all aware of the need in individual patients to carefully titrate doses of drugs which have a narrow therapeutic index.

Though the vast majority, if not all, of those in this audience readily accept the hypothesis that measuring serum concentrations of drugs with narrow therapeutic indices facilitates therapy, utilization of such measures at Parkland Hospital is low. This, in part, has been due to the technical reason that it has often been difficult to obtain assay results within a clinically useful time frame. This drawback has recently been addressed and rectified by the Clinical Pathology laboratory and, as a consequence, utilization of serum drug measurements should increase.

One of the objectives of this grand rounds is to convince you of the absolute need for obtaining measurements of drug concentrations with many of the drugs used regularly in our patient population. To convince you of this need, I think it important to examine the data which support the utility of using serum drug concentrations. I would intend to provide what I hope you will consider to be a convincing argument for their use by presenting data for aminoglycoside antibiotics, digoxin, phenytoin, and theophylline. In so doing, I will also demonstrate to you that predictive algorithms which are based on a priori estimation of patient handling of specific drugs are helpful as starting points, but these approaches are poor enough that they cannot stand alone. They require the additional step of measuring drug concentrations in individual patients to be used to formulate individualized dosing regimens.

Once one has obtained a measured serum drug concentration, there are a variety of methods by which this information can be utilized to individualize therapy and design dosing regimens for individual patients. All of these methods are mathematically complex and as such justify computer techniques for their utilization. I intend to demonstrate for you one or more computer programs we have designed with the assistance of the Medical Computing Resources Center with the goal of convincing you that their utility and ease of use is obvious. It will then be important to close this discussion with cautions one must follow in order to appropriately use serum drug concentrations. If one ignores simple principles related to drug disposition and response even the most sophisticated drug assays and computer programs become useless and potentially misleading.

JUSTIFICATION OF THE USE OF MEASURING SERUM DRUG CONCENTRATIONS

The relationship between the dose of drug one administers and the response elicited is subject to a variety of permutations as is simplistically illustrated in the schematic of Figure 1.

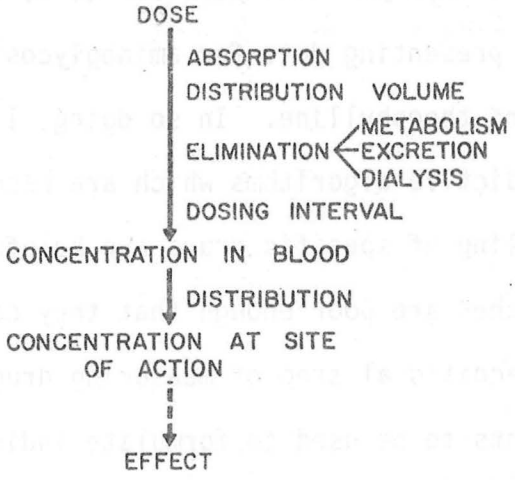


Fig 1: Schematic illustrating the multiple determinants of the relationship between dose of drug and effect.

Absorption, distribution, elimination and the frequency of administration of a dose influences concentration in serum. Disease states, drug interactions, and interindividual variability influence the kinetic parameters of absorption, distribution, and elimination, for which the clinician must compensate by modifying the dose and dosing interval to achieve the desired drug concentration in serum. It is important to note that though this discussion focuses on measuring serum concentrations of drugs, permutations can also exist between these concentrations and the effects observed in individual patients. Consequently, tailoring

of therapy to a drug concentration per se is inappropriate. One must, in addition, use clinical judgement and skills to assess the relationship in an individual patient of the measured serum drug concentration to the effect elicited. Serum drug concentrations should never be a substitute for clinical judgement.

It would seem intuitively obvious that the serum concentration of a drug would correlate better to response than would dose because of the many sources of variability among individuals in terms of the kinetic parameters that relate dose to concentration in serum. On the other hand, however, one might argue that disease and other influences on absorption, distribution and elimination can be quantified by appropriate studies, and thereby algorithms can be derived which will allow prediction in individual patients of their handling characteristics of a particular drug. Consequently, a dosing regimen could be designed which would predictably achieve the desired drug concentration in the individual patient. Indeed, there are a wealth of data in the literature (which seem to be expanding at an ever increasing rate) quantifying such relationships. Unfortunatley, however, considerable variability among individuals is still observed, even with those drugs about which we supposedly know the most. For example, it is clear that aminoglycoside antibiotics are solely eliminated by the kidney; therefore, one might presume that simple, quantitatively accurate relationships could be derived between measures of renal function and pharmacokinetic parameters for the various aminoglycoside antibiotics. Indeed, there are many papers in the literature deriving such relationships. If one collates these data, however, it is apparent that renal function can

only account for approximately 30% of the variability observed in handling of aminoglycoside antibiotics. Obviously, then, there is much that we still do not know, and predictive algorithms based solely on renal function are subject to considerable error. The fact that we are unable to accurately predict the quantitative handling of drugs in individual patients has been addressed by Vesell. Figure 2 is a schematic illustrating the interrelationships of various "host factors" that may influence drug response.

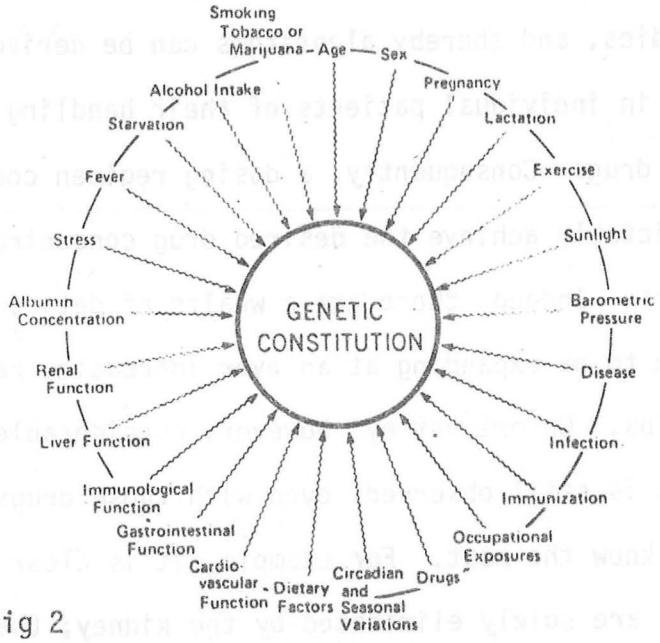


Fig 2

This circular design suggests the multiplicity of either well-established or suspected host factors that may influence drug response in man. A line joins all such factors in the outer circle to indicate their close interrelationship. Arrows from each factor in the outer circle are wavy to indicate that effects of each host factor on drug response may occur at multiple sites and through different processes that include drug absorption, distribution, metabolism, excretion, receptor action, and combinations thereof.

Figure 3 expands upon this schematic, further illustrating the complexity of determinants of individual handling of drugs, emphasizing that the best we may ever hope to accomplish from a predictive strategy is to achieve an approximate estimation (a "guestimate") of an individual patient's handling of a specific drug.

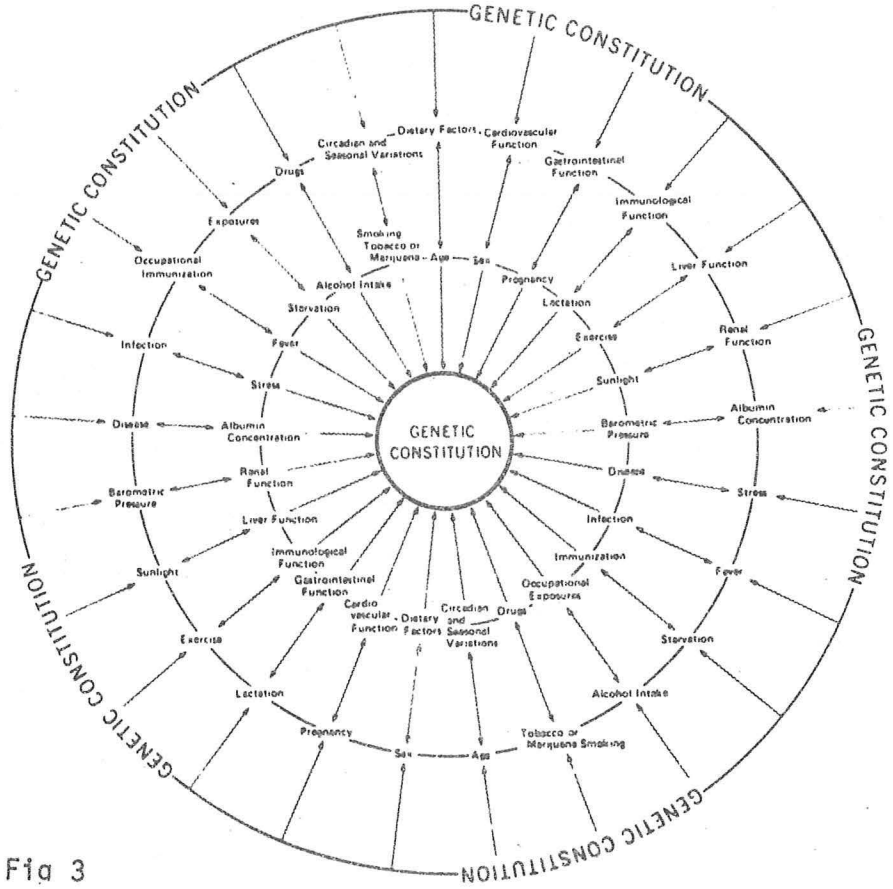


Fig 3

The concept of concentric outer circles was developed to emphasize the multiple possibilities that exist for interaction among host factors and to suggest that the magnitude of the impact of host factors on drug response may be modulated by genetic constitution. Because in most cases these specific interactions and modulations have not yet been investigated, much less firmly established, this design is largely speculative and intended to stimulate future research rather than to depict the current state of knowledge in the field.

Truly tailoring drug therapy to the individual patient, then, requires direct determinination of how that patient handles the drug in question; namely, quantifying the relationship between the dose administered and the concentration achieved. Though such an argument might appear intuitively obvious, it is important that we examine the data directly

addressing this question. Consequently, I will now present data with aminoglycoside antiobitics, digoxin, phenytoin and theophylline satisfying the criteria for utility of measuring serum drug concentrations outlined in Table 1.

TABLE 1

CRITERIA FOR UTILITY OF MEASURING SERUM DRUG CONCENTRATIONS

1. Serum concentration correlates better to response than does dose
2. Feedback from serum drug concentration value allows attainment of desired concentration and response better than do predictive algorithms
3. Using serum drug concentrations is cost effective

Aminoglycoside Antibiotics

Correlation of Dose and/or Serum Concentration to Response

It is clear that doses of aminoglycoside antibiotics relate poorly to the attained serum concentration. Figure 4 demonstrates the poor correlation between gentamicin dose and the change in gentamicin concentration resulting from that dose as observed by Goodman et al at this institution.

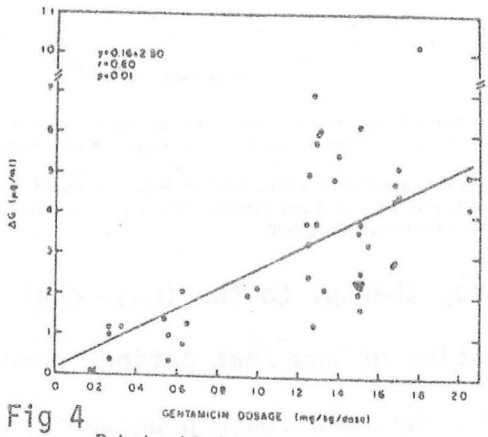


Fig 4 *Relationship between increment in gentamicin concentration in serum (ΔG) and dosage of gentamicin in 20 patients. The correlation coefficient (r) and the equation for linear regression calculated by the least squares method are shown. The P value was calculated for the hypothesis that the slope of the regression line is zero.*

Though the correlation is statistically significant, there clearly is considerable scatter in the data, verified by the correlation coefficient (r=0.6). Such variability would be unacceptable in patient care, in which more precise attainment of serum gentamicin concentrations will be demonstrated to be desired. Figure 5 shows similar data obtained by Schentag et al, again emphasizing the considerable scatter when one relates gentamicin dose to serum concentration.

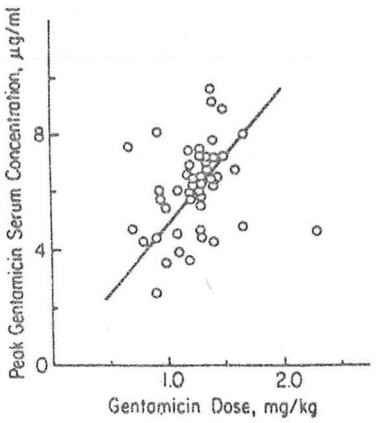


Fig 5

Relationship between peak serum concentrations and the administered maintenance dose of gentamicin (mg/kg body weight) in adults. Reproduced with permission of Journal of Pharmacokinetics and Biopharmaceutics from Schentag JJ, Jusko WJ, Vance JW et al. Gentamicin disposition and tissue accumulation on multiple dosing. 1977;5:559-77.

Similar data have been demonstrated repeatedly with all aminoglycosides in current use.

Though doses of aminoglycosides correlate poorly with serum concentrations, do the latter correlate with response? If not, the lack of a good relationship with dose may be irrelevant. Answering this question with antibiotics is considerably more difficult than with the other

drugs that will be considered today. However, Table 2 presents data from three separate papers indicating that serum concentrations, indeed, correlate to efficacy.

TABLE 2

ANTIBIOTIC EFFICACY AND SERUM CONCENTRATIONS

(J Infect Dis 129:187-193, 1974)

317 Patients
Peak serum titer ≥ 1:8, cure in ≥ 80%
Urinary tract infections, urine ≥ 1:4, cure in 90%

(Am J Med 61:493-497, 1976)

52 cases of Gr⁻ "breakthrough" bacteremia on appropriate antibiotics
Early breakthrough (< 72 Hr)
63% with subinhibitory concentrations
Late breakthrough (> 72 Hr)
35% with subinhibitory concentrations
39% compromised host
26% inadequate drainage

(Br Med J 1:477-481, 1974)

68 episodes of Gr⁻ bacteremia in 65 patients
Adequate peak, 84% cured
Inadequate peak, 23% cured

What about correlations of serum concentration to toxicity? Again, "hard" data are difficult to find. However, most clinicians are convinced that peak serum concentrations of gentamicin and tobramycin above 8-10 µg/ml (or the equivalent with other aminoglycosides) are associated with an increased incidence of ototoxicity and that sustained trough concentrations above 2 µg/ml may predispose to nephrotoxicity. In short, then, it appears that serum concentrations do correlate fairly well with response, whereas dose clearly correlates poorly with serum concentrations. In turn, therefore, dose must be assumed to relate poorly to response, either therapeutic or toxic. It probably comes as no great surprise, then, that data support the contention that achieving "target" serum concentrations of aminoglycoside antibiotics is useful, and one should design therapy towards attaining such target concentrations rather than using arbitrarily defined doses in individual patients.

Use of Serum Concentrations as Feedback to Attain Desired Target Concentrations

A variety of predictive algorithms have been derived to allow selection of an aminoglycoside dosing regimen based on demographic characteristics of individual patients. Early studies demonstrated that aminoglycosides were eliminated solely by the kidney, and initial guidelines focused on what now appear to be rather simplistic correlations of renal function with aminoglycoside pharmacokinetics. One of the earliest of these attempts was that of McHenry et al, commonly referred to as the "rule of eights". In 29 patients, these authors demonstrated that the half-life of gentamicin correlated closely with serum creatinine ($r=0.94$). In essence, half-life equalled the serum creatinine times 4. The authors recommended administering a dose every two times the half-life and consequently, then, the "rule of eights" refers to the administration of a "normal dose" of aminoglycoside to the patient at a dosing interval equal to the serum creatinine times 8. This method essentially represented a strategy of altering the frequency of administration while maintaing the dose constant (a variable frequency regimen).

Subsequently, Chan et al published a nomogram (Figure 6) which similarly related a recommended gentamicin dose to a patient's renal function, but these authors preferred a strategy of maintaining the dosing interval the same as in subjects with normal renal function while decreasing individual doses in those with renal compromise (a variable dosage regimen).

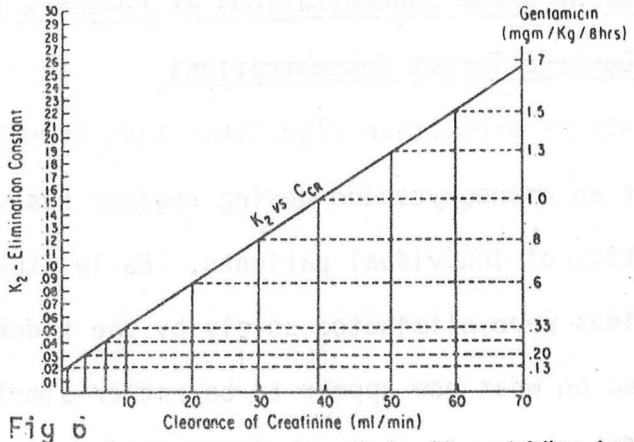


Fig 6 Dosage nomogram for patients with renal failure (see text for instructions for use).

For reasons that are unclear, these authors considered a normal creatinine clearance to be 70 ml/min/ 1.73m^2 and, by so doing, their nomogram recommended higher total doses than those which had been used previously. In their publication, they noted that 17 of 17 patients with life-threatening gram negative bacterial infections survived, and they attributed this success to the use of the variable dose strategy as opposed to the variable frequency strategy. In addition, however, the administration of a higher total dose may clearly have also played a role. The success rate implied that the nomogram provided appropriate serum concentrations in all patients in whom it was utilized. A subsequent study by Churchill et al examined the success of the Chan guidelines in 22 courses of therapy to 18 patients with creatinine clearances ranging from 6-65 ml/min. One hundred and thirty-three serum gentamicin concentrations were obtained in these patients with correlations derived between observed and predicted serum concentrations: for peak concentrations, r=0.70; for troughs, r=0.67. Though these correlations were significant, the relatively low r value is disconcerting when one considers the narrow therapeutic range of the aminoglycoside antibiotics.

The scatter implied should impart hesitancy in being confident that one could achieve a desired concentration in an individual patient.

Mawer et al published a nomogram using a variable frequency strategy which they also programmed on a small digital computer and, in 36 patients with a wide range of renal function, demonstrated a correlation of predicted to observed concentrations of 0.88. These authors demonstrated the nomogram to be superior to physician's intuition, and that the physician was able to achieve the target serum concentration in only 20 of 29 instances whereas the nomogram was successful in 39 of 39. In retrospect, however, it appears that this study must have included a select group of patients, for this dosing strategy has not met with similar success subsequently.

Hull and Sarubbi, and Sarubbi and Hull in this country and Dettli in Switzerland then formulated what is probably regarded as the best predictive algorithm for aminoglycoside therapy. The Hull and Sarubbi method utilized the strategy of maintaining a fixed maximum serum concentration of aminoglycoside. Then, both dose and dosing interval are modified to compensate for decreases in renal function and concomitantly minimize the potential impact of elevated trough serum concentrations. These authors published their first nomogram for gentamicin and then followed subsequently with a more general nomogram providing data for amikacin. Table 3 shows the relationships they derived for individualizing the pharmacokinetics of gentamicin.

TABLE 3

HULL AND SARUBBI METHOD OF PREDICTING INDIVIDUAL PHARMACOKINETICS-GENTAMICIN

Assume $V_d = 0.28$ L/Kg lean body weight

$K = 0.0024\ Cl_{Cr} + 0.01$

A key feature of their approach was the finding which has subsequently been verified by Reymann et al that aminoglycoside dosing is improved when one calculates dose as mg/kg of lean body weight rather than total body weight. In fact, in 120 patients the latter authors demonstrated no correlation of dose with concentration based on total body weight whereas the correlation was significant when dose was related to lean body weight. These data must be regarded, however, with a disclaimer that though this latter correlation was significant, considerable variability still occurred (r=0.626). The Sarubbi and Hull nomogram is provided in Figure 7 and as can be readily seen, this approach allows modification of both the dose and the dosing interval.

Dosing chart for aminoglycosides in adults

1. Select Loading Dose in mg/kg [IDEAL WEIGHT] to provide peak serum levels in range listed below for desired aminoglycoside.

Aminoglycoside	Usual Loading Doses	Expected Peak Serum Levels
Tobramycin Gentamicin	1.5 to 2.0 mg/kg	5 to 10 μg/ml
Amikacin Kanamycin	5.0 to 7.5 mg/kg	20 to 30 μg/ml

2. Select Maintenance Dose (as percentage of chosen loading dose) to continue peak serum levels indicated above according to desired dosing interval and the patient's corrected creatinine clearance.[a]

Percentage of Loading Dose Required for Dosage Interval Selected

C(c) cr (ml/min)	half life (hrs)[b]	8 hrs	12 hrs	24 hrs
90	3.1	84%	—	—
80	3.4	80	91%	—
70	3.9	76	88	—
60	4.5	71	84	—
50	5.3	65	79	—
40	6.5	57	72	92%
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10	20.4	24	34	56
7	25.9	19	28	47
5	31.5	16	23	41
2	46.8	11	16	30
0	69.3	8	11	21

[a]Calculate corrected Creatinine Clearance (C(c) cr as:
C(c) cr male = (140-age)/serum creatinine
C(c) cr female = 0.85 × C(c) cr male

[b]Alternatively, one half of the chosen loading dose may be given at an interval approximately equal to the estimated half life.

Fig 7

As each of the predictive dosing guidelines were published, considerable accuracy was demonstrated, usually in small patient groups which, in retrospect, were probably sufficiently homogenous to allow us to be deluded into thinking that the guidelines were more accurate predictors than they really were, and that they were sufficiently reliable to make measuring of serum concentrations superfluous. Studies in larger groups of patients, however, indicated the tremendous variability in individual handling of these drugs and subsequent unrealiability of the predictive algorithms. For example, Figure 8 from Zaske et al demonstrates the huge variability in half-life among 209 patients with normal renal function.

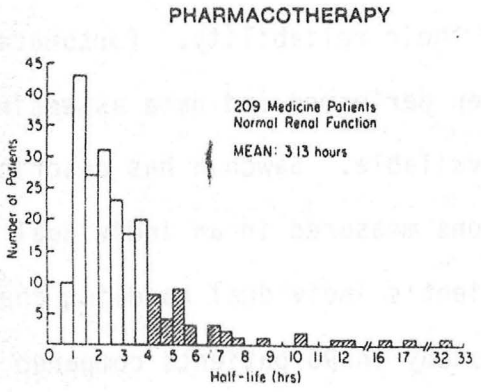


Fig 8

The serum half-life of gentamicin in 209 adult medicine patients with a normal serum creatinine. Reproduced with permission of Applied Therapeutics, Inc. from Zaske DE. Aminoglycosides. In Evans WE, Schentag JJ, Jusko WJ, eds. Applied Pharmacokinetics: principles of therapeutic drug monitoring. 1980;210-39.

Similarly, Table 4 presents data (also generated by Zaske) in over 600 patients demonstrating the tremendous variability in the dose required to achieve target concentrations, in half-life, and in volume of distribution in large heterogenous patient groups.

TABLE 4

VARIABILITY IN GENTAMICIN DOSING REQUIREMENTS
(Surgery 87:164-169, 1980 and JAMA 248:3122-3126, 1982)

	Customary	242 Surgical Patients	417 Elderly Patients
Dose (mg/kg/d)	3-5	0.7-12.4	0.3-22.0
Half-Life (hr)	2.5-4	0.4-13.4	0.3-32.7
Volume of Distribution (L/kg)	0.20-0.25	0.06-0.63	0.07-0.53

It is important to emphasize that all the previously discussed algorithms assumed volume of distribution of aminoglycoside antibiotics to remain constant (see Table 3). This is clearly not the case (see Table 4).

Consequently, it becomes critically important to assess how well predictive algorithms perform in large groups of unselected patients before accepting their reliability. Fortunately, comparative studies have recently been performed and data assessing reliability in the "real world" is thus available. Sawchuk has described a method by which serum drug concentrations measured in an individual patient are used to determine that patient's individual handling characteristics for that drug. A recent study in 96 patients compared this method to that of the "rule of eights", the Chan nomogram, and the approaches of Sarubbi and Hull and of Dettli. In general, the predictive algorithms resulted in 50% of the concentrations being inadequate, and in 20%, trough concentrations were >2 µg/ml.

These data are shown graphically in Figure 9 in which the Sawchuk method is referred to as "individual".

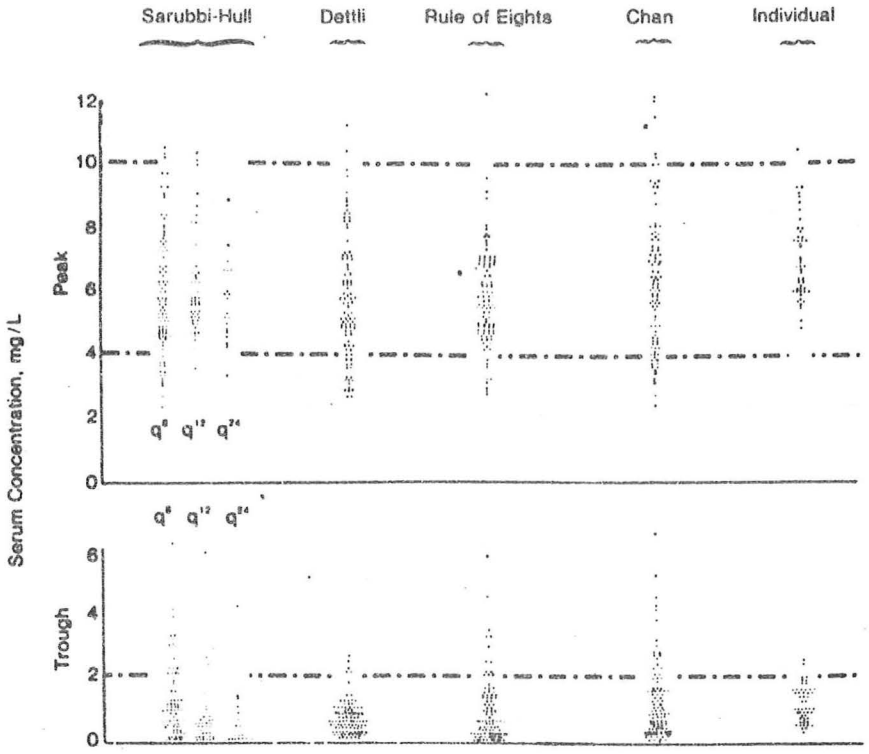


Fig. 9

Serum concentrations for four predictive dosing methods (calculated) and individualized method (measured). Individualized method produced peak concentrations of 4 to 10 mg/L and troughs of 2 mg/L or less in significantly more patients (94%) than all predictive methods ($P<.01$); q^8 indicates doses at eight-hour intervals; q^{12}, at 12-hour intervals; and q^{24}, at 24-hour intervals.

Clearly, the latter approach was the only method that allowed attainment of target serum concentrations. Another recent study compared the Sawchuk method with that of Hull and Sarubbi and with that of Tozer (Figure 10), another method assuming the volume of distribution for gentamicin to be constant.

TOZER METHOD OF PREDICTING INDIVIDUAL PHARMACOKINETICS

Assume constant V_d from population data

$$t_{1/2}\ \text{patient} = \frac{t_{1/2}\ \text{normal}}{f_e\,(K_f - 1)} + 1$$

where f_e = fraction of drug excreted unchanged in urine

$$K_f = \frac{\text{patient's creatinine clearance}}{\text{normal creatinine clearance}}$$

For Gentamicin:

$$t_{1/2}\ \text{patient} = \frac{2}{0.97\left(\frac{Cl_{cr}}{120} - 1\right)} + 1$$

V_d = 0.28 L/Kg lean body weight

Fig 10

A graphic representation of the relationship between predicted and actually measured serum gentamicin concentrations is demonstrated in Figure 11 for the Tozer method, Figure 12 for the Hull and Sarubbi method, and Figure 13 for the Sawchuk method with the correlations for peak and trough concentrations presented in Table 5.

Figure 3. Relationship between predicted and measured serum gentamicin concentration (SGC) using the Tozer method. Data represent 17 pairs of trough (O) ($r = 0.30$, $p > 0.05$) and peak (●) ($r = 0.38$, $p > 0.05$) SGCs. Solid line represents line of identity.

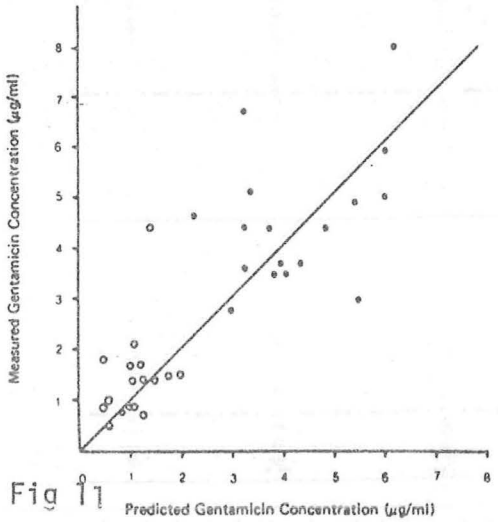


Fig 11

Figure 4. Relationship between predicted and measured serum gentamicin concentration (SGC) using the Hull method. Data represent 17 pairs of trough (O) ($r = 0.33$, $p > 0.05$) and peak (●) ($r = 0.38$, $p > 0.05$) SGCs. Solid line represents line of identity.

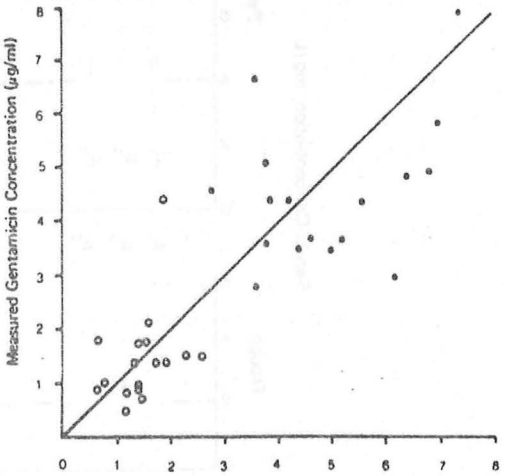


Fig 12

Figure 1. Relationship between predicted and measured serum gentamicin concentration (SGC) using the Sawchuk-Zaske method. Data represent 17 pairs of trough (O) ($r = 0.91$, $p < 0.01$) and peak (●) ($r = 0.73$, $p < 0.01$) SGCs. Solid line represents line of identity.

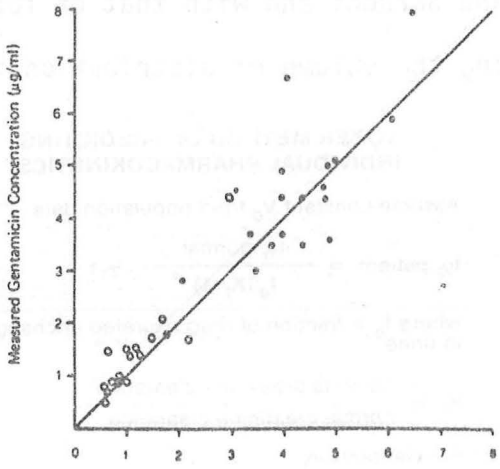


Fig 13

TABLE 5

CORRELATION OF OBSERVED TO PREDICTED SERUM GENTAMICIN CONCENTRATIONS

(Clin Pharm 1:361-365, 1982)

Method	Peak	Trough
Sawchuk and Zaske	0.73	0.91
Tozer	0.38	0.30
Hull and Sarubbi	0.38	0.33

Though the correlation observed with the Sawchuk method is still of a magnitude to indicate considerable scatter among patients (see Figure 13), it is clear that using measured concentrations in an individual patient to determine that patient's handling characteristics and, thereby, devise individualized dosing regimens is vastly superior to using predictive algorithms. One other approach has been tested for aminoglycoside therapy. A Bayesian statistical approach (which will be discussed in more detail subsequently) implemented by Jelliffe has been reported (in abstract form) to be particularly accurate, though no data were provided.

Cost-Effectiveness of Monitoring Serum Drug Concentrations

Though the foregoing data clearly demonstrate a better correlation of serum aminoglycoside concentration to response than of dose to response, and they demonstrate the absolute necessity of using measured concentrations in an individual for dosing regimen design, one cannot *a priori* conclude cost efficacy. The assay procedure for any drug measurement has a finite and not inexpensive cost and its interpretation for development of an individualized dosing regimen requires personnel time. It is conceivable, therefore, that such costs might outweigh the benefits derived. As one might suspect, studies of cost-effectiveness are very difficult. A hint that individualization of aminoglycoside dosing may be cost justified can be found in a report by Solem et al of 5 burn patients with ecthyma gangrenosum which heretofore had been universally fatal. This paper described the survival of 4 of the 5 patients when therapy was individualized based on feedback from measured serum gentamicin concentrations. It was noted that these patients required 12-30 mg/kg/day of gentamicin as opposed to the usual recommendation of 3-5 mg/kg/day in subjects with normal renal function. This fact is not particularly

surprising in view of the data in the literature demonstrating the increased renal excretion of aminoglycosides in patients with burns, but it serves to emphasize that using serum drug concentrations as guides can allow administration of such large doses not only safely but in a manner which clearly results in additional efficacy. Bootman et al performed a more rigid cost-benefit analysis of individualizing gentamicin dosage regimens in burn patients. Thirty-nine controls were compared to 66 patients. In the latter therapy was based on measures of serum concentrations in individual patients. Doing so resulted in administration of significantly larger doses at considerably shorter dosing intervals and culminated in a survival rate twice that of the control group (Table 6).

TABLE 6

BENEFITS OF INDIVIDUALIZING GENTAMICIN DOSING In Burn Patients

(J Pharm Sci 68:267-272, 1979)

	Controls	Individual Kinetics
number	39	66
% Burn	47.0 ± 19.8	50.7 ± 21.1
Dose (mg/kg/d)	4.4 ± 4.5	7.4 ± 2.8
Dosing Interval (hr)	8.1 ± 2.9	5.3 ± 1.7
Survived (%)	33.3	63.6

Notwithstanding the increased survival alone, these authors also assessed the cost-benefit of individualizing therapy by calculating the expenses of the increased hospitalization time of the survivor's weighed against the productivity losses of those who died, etc. They found that an individualized approach to therapy was indeed cost-effective. As will be noted subsequently, comparable data for most other drugs are still forthcoming.

In summary, for aminoglycoside antibiotics, all criteria for utility of measuring serum concentrations are met. It is clear that appropriate use of aminoglycoside antibiotics requires monitoring of serum concentrations and subsequent individualization of therapy. The best manner in which to do this will be presented subsequently.

Digoxin

Correlation of Dose and/or Serum Concentration to Response

Digitalis glycosides represent one of the few drugs for which solid data demonstrate that measuring serum concentrations beneficial. The original paper by Smith and Haber describing use of serum digoxin concentrations showed that dose of digoxin did not correlate with digitalis toxicity whereas assessing toxicity relative to serum concentrations showed a significant difference between toxic and non-toxic patients. Figure 14 presents the data from their original paper showing that patients with digoxin toxicity received the same dose of digoxin while their serum concentrations were significantly different.

	Nontoxic	Toxic	P*
n	131	48	
Digoxin dosage, mg/day			
Mean ±SD	0.31 ±0.19	0.36 ±0.19	NS
Range	0.0625–1.0	0.125–1.0	
Serum digoxin concentration, ng/ml			
Mean ±SD	1.4 ±0.7	3.7 ±1.0	<0.001
Range	0.3–3.0	1.6–13.7	

* *t* test; NS denotes $P > 0.05$.

Fig 14: Relationship between digoxin dose and toxicity compared to that between serum concentration and toxicity.

Serum concentrations were a better correlate of toxic response than was dose; however, as shown in Figure 15 from the same study, there clearly was considerable overlap between toxic and nontoxic patients.

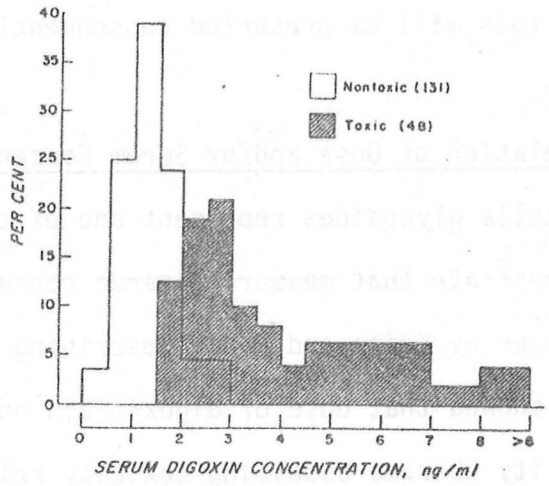


Fig 15: Overlap of serum digoxin concentrations of toxic and non-toxic patients.

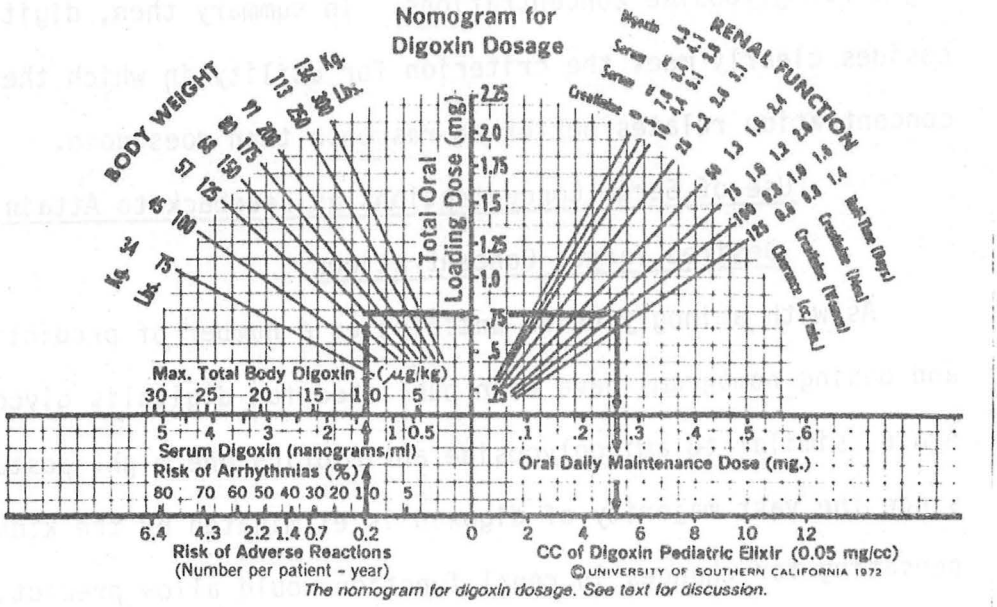
As emphasized at the start of this discussion, this fact demonstrates the critical importance of assessing the relationship between concentration and response with clinical criteria in each patient. Some patients may have digoxin toxicity with serum concentrations in the "therapeutic range" whereas others may require "toxic levels" to achieve a beneficial response. Using serum concentrations can help discriminate toxic from nontoxic patients, but their main utility will be as feedback allowing design of individually tailored dosing regimens such that the clinician can achieve whatever concentration he deems from clinical criteria to be most appropriate in his patient. A variety of studies subsequent to those of Smith and Haber have confirmed their data. The

impact of using serum digoxin concentrations on morbidity and mortality will be addressed subsequently in considering the cost-benefit of measuring serum glycoside concentrations. In summary then, digitalis glycosides clearly meet the criterion for utility in which the serum drug concentration relates better to response than does dose.

Use of Serum Concentrations as Feedback to Attain Desired Target Concentrations

As with aminoglycoside antibiotics a number of predictive algorithms and dosing nomograms have been published for digitalis glycosides. Again, similar to aminoglycoside antibiotics one might postulate that since the vast majority of digoxin is eliminated by the kidney, compensating for changes in renal function would allow predictive algorithms to have considerable accuracy. This has not proved to be the case. Part of the reason may be that we now know that digoxin is not only filtered by the kidney but also has secretory and reabsorptive components of renal excretion; their quantitative balance in an individual patient is difficult, if not impossible, to predict. Consequently, though nomograms are useful as starting points for therapy with digitalis glycosides, they must be supplemented with measured serum concentrations.

Perhaps one of the most frequently used nomograms is that of Jelliffe (Figure 16) which allows compensation for prior dosing, body size, and renal function.



The nomogram for digoxin dosage. See text for discussion.

Fig 16

A recent analysis in 85 patients by Jones et al assessed the aaauracy of 12 different digoxin dosing algorithms (including Jelliffe's). All of these algorithms tended to underestimate the digoxin dose necessary to achieve the desired concentration, and the correlation coefficients relating predicted to observe concentrations ranged from -0.393 to 0.389 (Table 7).

TABLE 7

EVALUATION OF 12 METHODS FOR DIGOXIN DOSING IN 85 PATIENTS*
(J Clin Pharmacol 22:543-550, 1982)

Method	Correlation Coefficient
Jelliffe	0.211
C-Bar	0.223
Paulson	0.278
Koup	0.289
Koup/CHF	0.354
Gault	0.302
Sumner	0.182
Dobbs	0.332
Dobbs	0.258
Dobbs	0.279
Shapel	-0.393
Wagner	0.338

*Siersbaek-Nielsen nomogram for renal function;
Used lesser of actual or ideal body weight

Clearly, even the best of these algorithms is poor. The authors concluded that since all methods underestimated the needed digoxin dose, they were relatively safe but should not be used as anything other than a starting guideline. In stark contrast, several studies have demonstrated the ability to use measured serum concentrations of digitalis glycosides in individual patients to tailor therapy to that individual. In turn, studies have also demonstrated that use of computers allows better success than does the intuition of the physician. Sheiner has been a pioneer in this area and has developed much of the computer technology utilized in creating feedback loops to individualize therapy. As shown in Figure 17 from one of his papers, a computer outperforms a physician using serum concentration measurements, using two concentrations is better than one, and that it if a computer technique is not available, the physician's intuition is better than nothing.

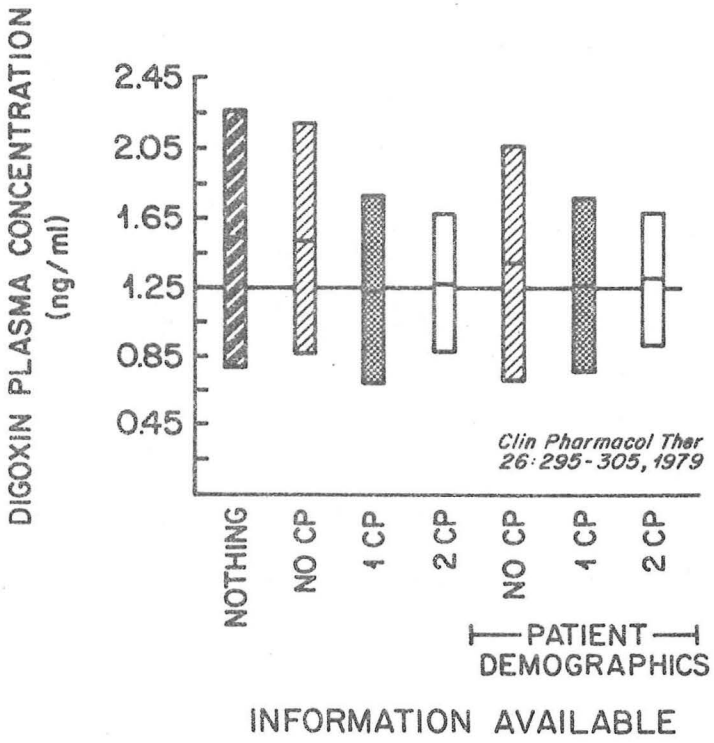


Fig 17: Improvement in achieving digoxin target concentrations with various strategies. Patient demographics with or without concentrations in plasma (CP) offers little improvement whereas measured concentrations improve accuracy with two concentrations better than one.

Similarly, Rich et al compared 25 control subjects to 22 patients in whom computer assistance was used. The intuitive judgement of the physician was able to make appropriate dose adjustments in 14%, compared to 43% for the computer, and the desired serum concentration was achieved intuitively in only 45%, compared to 80% with a computer. It is important to note that the computer technique used in this latter study is considerably less sophisticated than that developed by Sheiner. Another way of expressing the utility of using computer feedback is shown in Figure 18, again from Sheiner's work, where the use of computer feedback is able to decrease by 75% the number of patients outside the therapeutic range. The method used by Sheiner is that of a Bayesian feedback loop which, with digitalis glycoside therapy, appears to be the best method currently available. This was also noted above with aminoglycoside antibiotics.

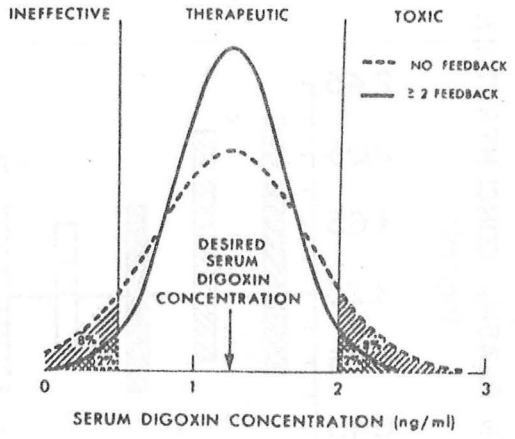


Fig 18: Ability of a computer using Bayesian feedback techniques to decrease the % of digoxin concentrations outside the therapeutic range.

Cost-Effectiveness of Monitoring Serum Drug Concentrations

Again, it has been clearly demonstrated that the proper use of serum digoxin concentrations can improve the ability to achieve a desired concentration. However, is this cost effective? Two separate bodies of information attest to the utility of this therapeutic strategy. On the one hand, as illustrated in Figure 19, it appears that digitalis toxicity is associated with considerable increases in morbidity over and above those patients receiving digitalis alone.

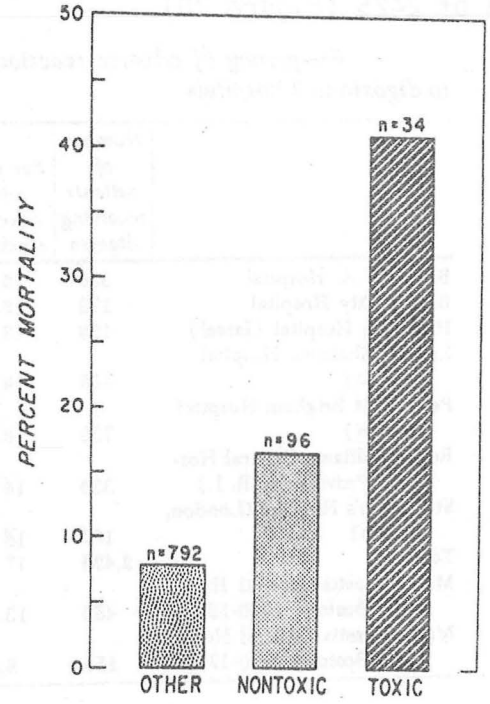


Fig 19: Adverse impact of digoxin toxicity on mortality.

As a consequence, it is not an unreasonable hypothesis to presume that decreasing the incidence of digitalis toxicity should decrease morbidity and mortality from this drug. The latter postulate has not been directly proven. However, considerable data demonstrate that use of serum digoxin concentrations does, in fact, decrease the incidence of digitalis toxicity.

In one of Jelliffe's early studies, a decrease in the incidence of digitalis toxicity from 35.5 to 12.5% occurred with implementation of serum digoxin concentration measurements for individualizing digoxin therapy. Smith noted in a recent review that studies from various authors in approximately 1500 patients before the ability to use serum digoxin concentrations to guide therapy was prevalent reported an incidence of digoxin toxicity ranging from 13.3 to 29%. Similarly, Koch-Weser et al reported an incidence of digitalis glycoside toxicity ranging from 13.1 to 19.4% in 7 different hospitals encompassing a total patient population of 2425 (Figure 20).

Frequency of adverse reactions to digoxin in 8 hospitals

	Number of patients receiving digoxin	*Per cent with adverse reactions*
Boston V.A. Hospital	330	15.2
Boston City Hospital	273	16.2
Hadassah Hospital (Israel)	128	13.1
Lemuel Shattuck Hospital (Boston)	485	19.4
Peter Bent Brigham Hospital (Boston)	736	16.9
Roger Williams General Hospital (Providence, R. I.)	336	14.3
St. Joseph's Hospital (London, Ontario)	137	16.8
Total	2,425	17.0
Massachusetts General Hospital (Boston) 1966-1968	459	13.9
Massachusetts General Hospital (Boston) 1970-1972	253	5.9

Fig 20

This incidence of toxicity, they noted, was similar to that at their own hospital (Massachusetts General Hospital) of 13.9% in 459 patients in the era prior to utilization of serum digoxin concentrations. After implementation of such measures, however, the incidence of toxicity in 253 patients fell to 5.9%. These same authors compared the incidence of digitalis toxicity at MGH to that at Peter Bent Brigham Hospital. At

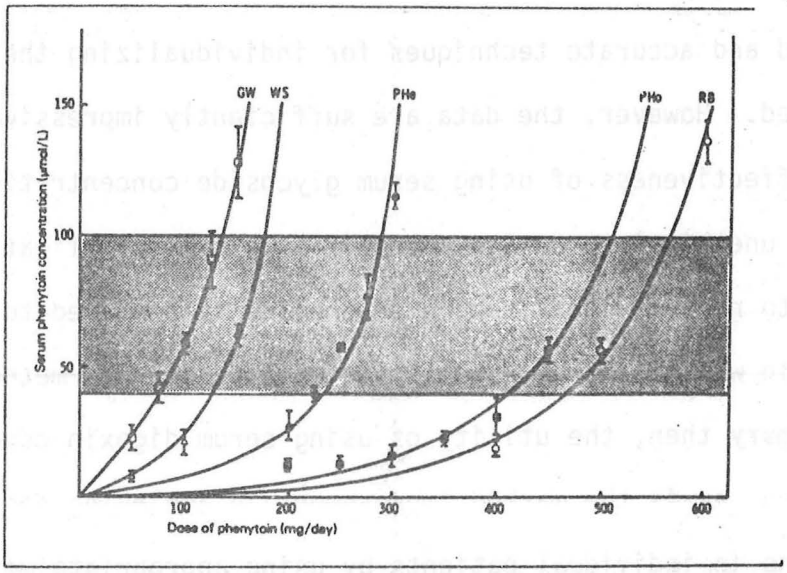
the former, 40% of patients receiving digoxin were monitored with determination of serum digoxin concentrations as compared to 12% at Peter Bent Brigham Hospital. At the latter, 10% of 272 patients developed digitalis toxicity compared to 4% of the 291 patients at Massachusetts General Hospital. It is important to note that these studies demonstrating decreases in incidence of digitalis toxicity used a crude approach for dose adjustment based on the measured serum glycoside concentration; namely, physician intuition. It is not unreasonable to suspect that even more impressive differences would be realized if the most sophisticated and accurate techniques for individualizing therapy had been utilized. However, the data are sufficiently impressive to verify the cost effectiveness of using serum glycoside concentrations, and it would now be unethical to design a trial in which control patients were allocated to no individualization of therapy as compared to an experimental group in which the most sophisticated and accurate methods were used. In summary then, the utility of using serum digoxin concentrations is verified, as is the marked improvement in achieving desired serum concentrations in individual patients by using appropriate methodology to individualize therapy. As was observed with aminoglycoside antibiotics, predictive algorithms serve as helpful starting points but cannot be used for chronic care of patients.

Phenytoin

Correlation of Dose and/or Serum Concentration to Response

Phenytoin is a particularly difficult drug to use, for in addition to its narrow therapeutic range, it obeys dose dependent kinetics (also referred to as saturable or Michaelis-Menten kinetics). Phenytoin is one of the few drugs which, at clinically used doses, has the capacity

for saturating pathways of elimination. Consequently, within the therapeutic range, small increments in dose can often lead to large increases in serum concentration with concomitant decreases in the overall elimination rate, prolongation of the half-life, etc. This phenomenon is illustrated in Figure 21 taken from data of Richens and Dunlop.



Relationship between phenytoin dose and serum concentration in 5 epileptic patients. Each point represents the mean ± SD of 3 to 6 seperate estimations of the serum concentration in steady-state. The curves were fitted by computer using the Michaelis-Menten equation. The stippled area indicates the therapeutic range of serum concentrations (a slightly higher upper limit is given than suggested in the text) [after Richens and Dunlop: Lancet 2: 247-248 (1975b)].

Fig 21

The curvilinear nature of the relationship between the dose of phenytoin and the concentration achieved is obvious, as is the tremendous variability among patients in terms of this relationship. Consequently, one would predict a very poor relationship between dose of phenytoin and the concentration achieved.

That this is the case is supported by numerous studies, one example of which is depicted in Figure 22.

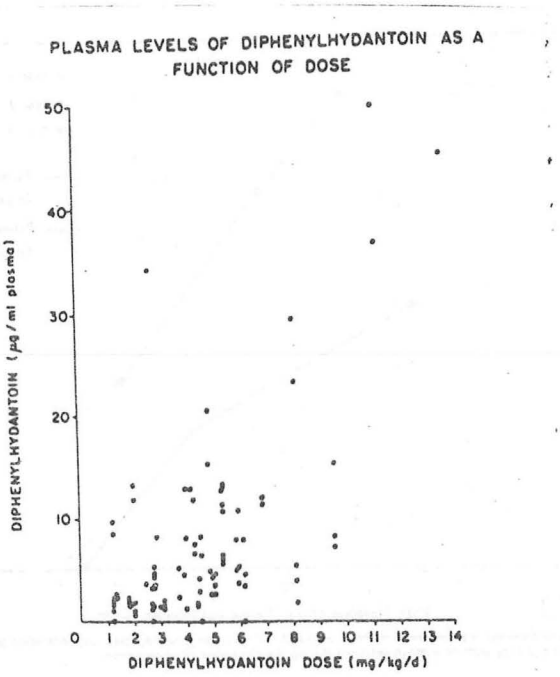


Fig 22

The tremendous variability in this relationship is obvious.

If measuring serum concentrations in patients is to be justified, one must demonstrate a good correlation between serum concentrations and both efficacious and toxic response. Correlations of phenytoin concentrations to efficacy have been shown by Buchthal et al, but probably most impressively by Lund who assessed this relationship in 32 patients followed prospectively for 3 years.

His data are depicted in Figure 23 which clearly shows a decrease in seizure frequency with increasing phenytoin concentrations within the therapeutic range.

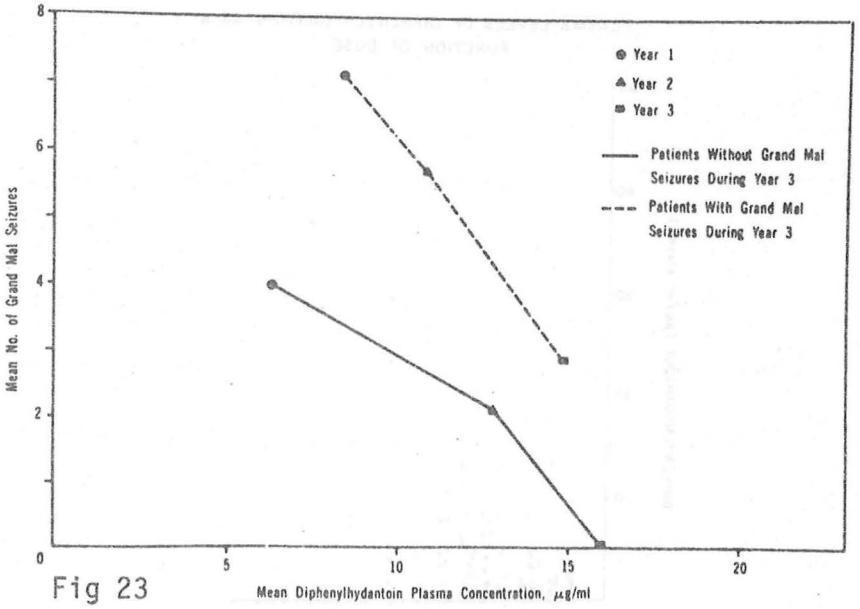
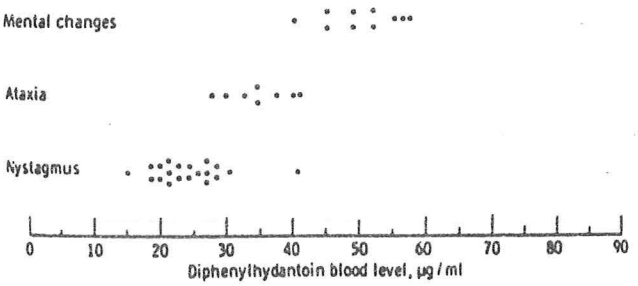


Fig 23

Relationship between annual mean number of grand mal seizures and the mean concentration of diphenylhydantoin in two groups consisting of patients with or without seizures during the third year of observation.

As should be apparent, generation of this type of data is exceedingly difficult because of the spontaneous variability of seizure frequency among patients. The fact that a 3 year prospective study was required demonstrates the difficulty encountered in this general area of relating serum concentrations to efficacy while, on the other hand, it has always been much easier with most drugs to relate serum concentrations to toxicity. This holds true with phenytoin and has been documented in large numbers of patients. For example, Haerer and Grace assessed 282 phenytoin concentrations in 166 out-patients demonstrating a very close correlation of serum concentration to toxicity. The two investigators cited previously who documented correlations with efficacy have also shown correlations of serum concentration with toxicity, and finally,

Kutt, who has been an active investigator in this field since the early 1960's, has produced data such as that shown in Figure 24 clearly relating toxicity to serum phenytoin concentrations.



The onset of central nervous system side-effects in relation to phenytoin concentration is shown above. Far-lateral nystagmus is most frequently observed with a concentration of 20 µg/ml; however, this symptom is first observed occasionally at much lower or higher concentrations. Ataxia and gross mental changes are usually evident at concentrations of greater than 30 and 40 µg/ml, respectively. From reference 49.

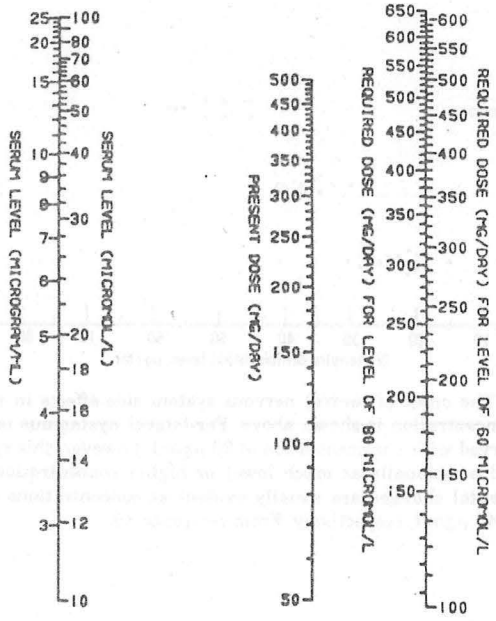
Fig 24

Again, then, phenytoin represents a drug for which serum concentrations correlate better to response than does dose.

Use of Serum Concentrations as Feedback to Attain Desired Target Concentrations

As with other previously discussed drugs, various predictive algorithms have been proposed for phenytoin dosing. It is important to note that since phenytoin follows Michaelis-Menten kinetics, the pharmacokinetic parameters that one must derive for individual patients are K_m and V_{max} just as in enzyme biochemistry. As with the pharmacokinetic parameters of other drugs, these parameters for phenytoin are subject to tremendous interindividual variability.

One of the first predictive algorithms, and one which is still frequently used, is that of Richens and Dunlop as illustrated in Figure 25.



Nomogram for adjusting phenytoin dosage: a detailed explanation is given in our article (Aug. 9, p. 248).

Fig 25

This method requires one measured serum concentration in each patient. Those methods of strictly a predictive nature have proved to be miserable in their ability to attain desired serum concentrations and will not be discussed. The limitations of this algorithm are that it assumes an average, constant K_m and therefore individually adjusts only V_{max}.

A different approach was described by Mullen with a graphical method in which two dose-serum concentration pairs at steady state are needed (Figures 26 and 27).

MULLEN NOMOGRAM FOR PHENYTOIN

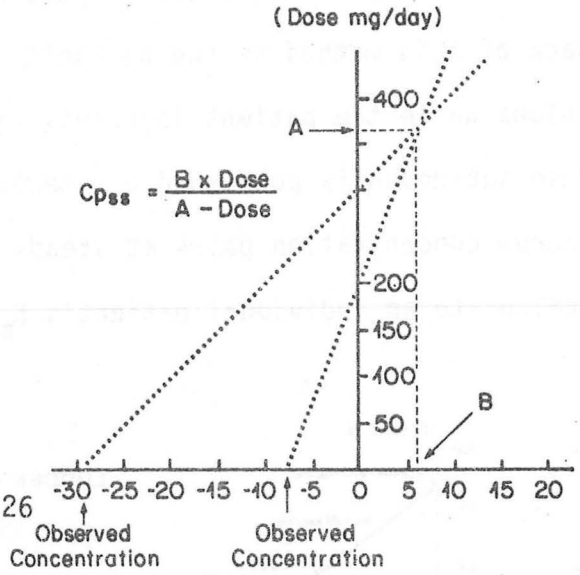


Fig 26

CLIN. PHARMACOL. THER. 23:228-332, 1978

MULLEN NOMOGRAM FOR PHENYTOIN

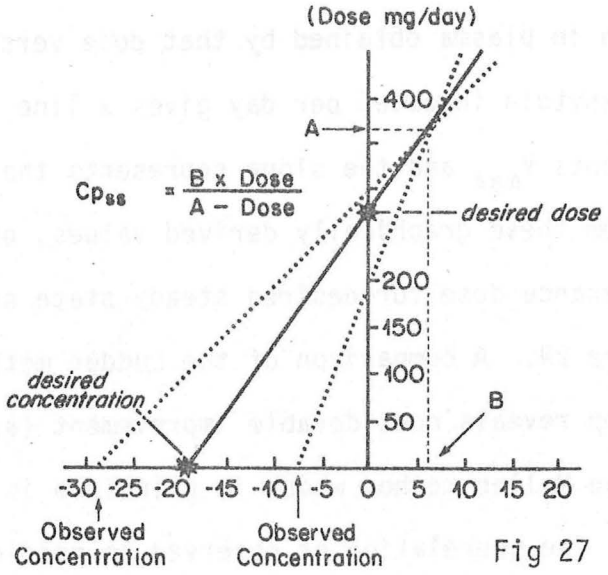


Fig 27

CLIN. PHARMACOL. THER. 23:228-332, 1978

Each dose-concentration pair can be used to construct a line as shown in Figure 26. The intersection of these two lines plus the desired concentration for the patient can be used to construct another line, the intersection of which with the Y-axis defines the needed dose (Figure 27). The drawback of this method is the necessity for 2 steady state serum concentrations while the patient is receiving different doses of phenytoin. Ludden subsequently published a somewhat similar method in which two dose-serum concentration pairs at steady state can be used graphically to calculate an individual patient's K_m and V_{max} (Figure 28).

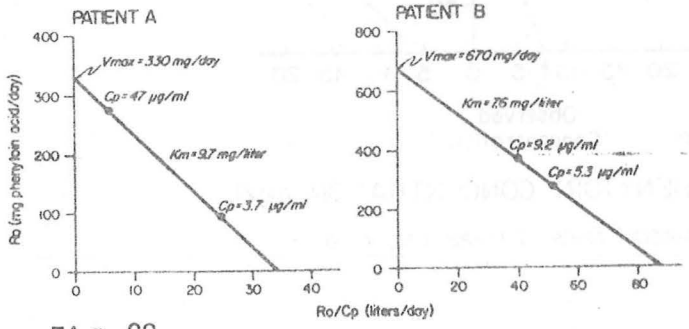


Fig 28
Graphic estimation of individual Vmax and Km values for phenytoin.

LUDDEN METHOD FOR PHENYTOIN DOSING

Determine individual patient's V_{max} and K_m graphically using two pairs of Dose/Cp_{ss}
Calculate maintenance dose for desired Cp_{ss}:

$$R_o = \frac{V_{max}\,Cp}{K_m + Cp}$$

Fig 29

A plot on the X-axis of milligrams of phenytoin taken per day divided by the concentration in plasma obtained by that dose versus on the Y-axis the amount of phenytoin ingested per day gives a line in which the Y intercept represents V_{max} and the slope represents the negative of K_m (Figure 28). From these graphically derived values, one can then calculate the maintenance dose for desired steady state serum concentration as shown in Figure 29. A comparison of the Ludden method to that of Richens and Dunlop reveals considerable improvement (as might also be suspected with the Mullen method which in principle is very similar to that of Ludden). The correlation of observed to predicted serum phenytoin concentrations using the Richens and Dunlop method yielded an r

value of 0.360 as compared to Ludden's method resulting in a correlation coefficient of 0.824. Yet another method has been described and tested in 49 patients. This, again, represents the Bayesian feedback approach, the principles of which were originally developed by Sheiner. In a study by Vozeh et al, 75 steady state serum concentrations in 32 patients were used to determine V_{max} and K_m for a population of average patients; these prospective values were 7.22±0.25 mg/kg/day and 4.44±0.4 µg/ml. Results of this study are depicted in Figures 30 and 31.

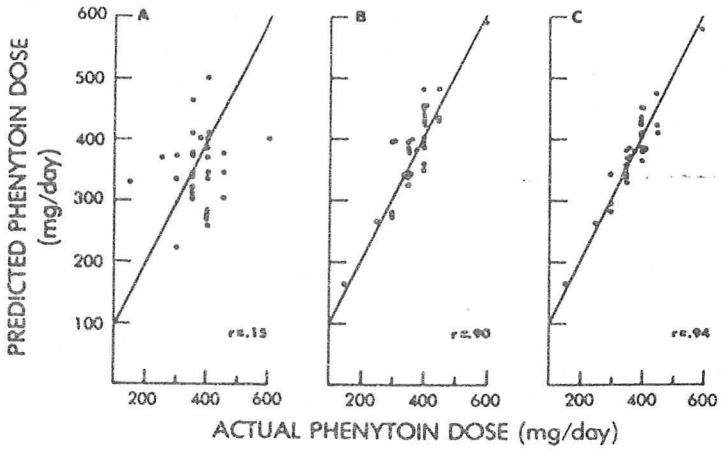


Fig 30: Comparison of different methods of phenytoin dosing. Panel A represents use of population based parameter estimates. Panel B represents the Richens and Dunlop nomogram using one measured serum concentration. Panel C represents the Bayesian method using one serum concentration.

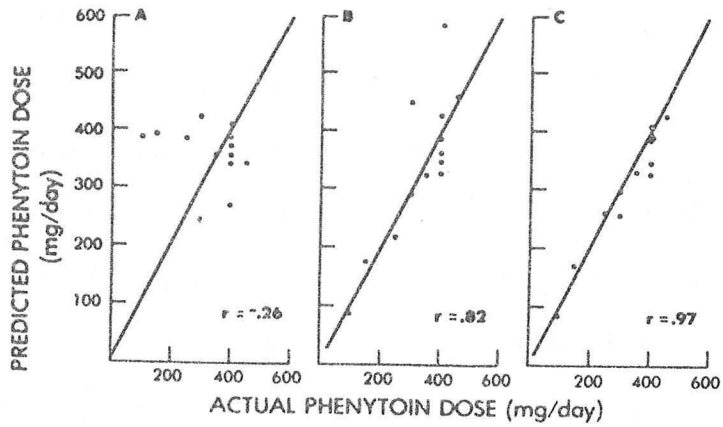


Fig 31: Comparison of different methods of phenytoin dosing. Panel A represents use of population based parameter estimates. Panel B represents Ludden's method using two measured serum concentrations. Panel C represents the Bayesian method using two serum concentrations.

In Figure 30, the left hand panel, (marked A) depicts the relationship between the actual phenytoin dose required to achieve the desired steady state plasma concentration versus the predicted phenytoin dose using estimates based on average population data. In other words, panel A represents a predictive algorithm without feedback from measured blood concentrations. Clearly, the correlation coefficient here (r=0.15) is unacceptably low. The middle panel represents the method of Richens and Dunlop in which vast improvement is observed (r=0.90). The far right panel illustrates the same patients in whom the Bayesian feedback approach was used with feedback from one measured serum concentration. The Bayesian approach came approximately 30% closer to the actual dosage than did the Richens and Dunlop method. Figure 31 is a similar depiction with, again, the leftward panel (labelled A) representing use of population derived parameters; i.e., a predictive algorithm without feedback from measured serum concentrations. The middle panel represents results using the method of Ludden in which two dose-serum concentration pairs at steady state were used. This method is clearly superior to not using serum concentrations. Again, the far right panel represents the Bayesian approach which comes approximately 60% closer than Ludden to achieving the desired phenytoin dose using two serum concentrations for feedback. Again then, it appears that feedback methods using the Bayesian approach are superior to other techniques for individualizing therapy with phenytoin.

Cost-Effectiveness of Monitoring Serum Drug Concentration

As with other drugs previously discussed, one must also ask the question as to whether or not use of measures of serum phenytoin concentrations or those of other antiepileptic drugs is cost effective.

The current literature accepts as a matter of course that therapy is inadequate unless serum phenytoin measurements are obtained, though no direct cost-benefit analysis exists. Kutt and Penry have written that use of blood levels has decreased the incidence of poorly controlled seizures by 50%, and one must presume that this benefit far outweighs the cost of the methods employed, notwithstanding additional benefits derived by avoiding toxicity. I think it is a reasonable assumption that such approaches are cost effective with phenytoin and, therefore, all of the predefined criteria for utility of using measures of serum concentration are fulfilled for phenytoin.

Theophylline

Correlation of Dose and/or Serum Concentration to Response

Clear-cut relationships have been demonstrated between serum concentrations of theophylline and both efficacious and toxic effects. As with other drugs discussed previously, correlation of dose with serum concentration is very poor. Figure 32 presents data from Weinberger et al demonstrating huge variability among patients.

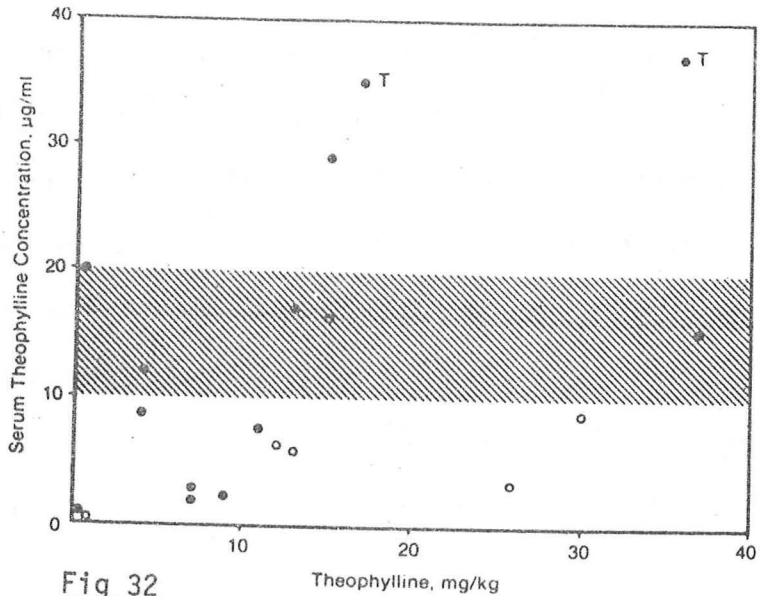


Fig 32
Relationship between initial serum theophylline concentrations and theophylline dosage history during previous 24 hours. Open circles indicate children; closed circles, adults; T, theophylline toxicity; shaded area, therapeutic range.

Similar results were obtained in 48 subjects by Hendeles et al (Figure 33).

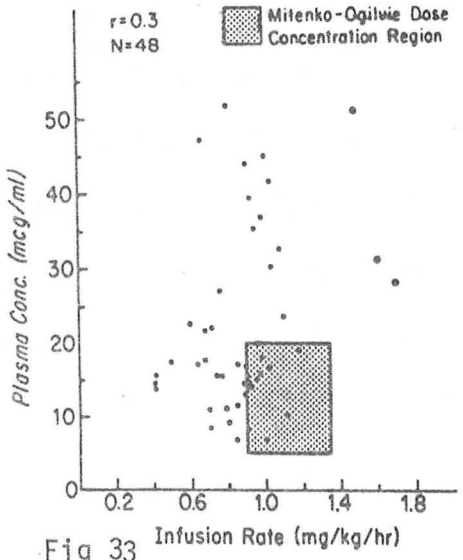


Fig 33 Dose Relationship with Plasma Concentration
patients who received an excessive dose

This figure is of additional interest, for it includes in the shaded area the dosing recommendations and the expected concentrations that Mitenko and Ogilvie demonstrated in one of the signal papers assessing the relationship between serum theophylline concentrations and response. These authors published guidelines for loading dose and a maintenance infusion for theophylline to maintain serum concentrations between 8 and 20 µg/ml. Unfortunately, their data were obtained from a homogenous population group; namely, young, normal volunteers or asthmatics with no concomitant disease, a population group which has a relatively high metabolic clearance rate of theophylline compared to the overall population to whom this drug is administered. Implementation of these authors' recommendation resulted in considerable numbers of patients developing toxicity. Figure 33, therefore, has dual messages--one, the extremely poor correlation of theophylline dose to serum theophylline

concentration and secondly, the inability of a rigid, predictive algorithm to attain desired concentrations. That this latter point should be obvious is dramatically documented by a recent review of Jusko et al who collated the variety of possible influences on theophylline handling. Their cascade is reproduced in Figure 34 demonstrating the inordinate complexity involved in deciphering <u>a priori</u> how an individual patient will metabolize theophylline.

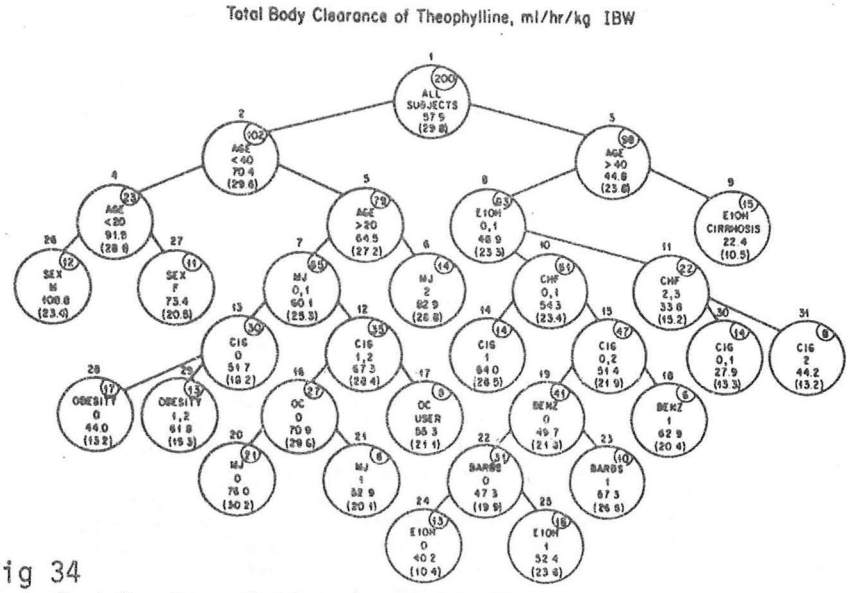


Fig 34

Cascade of factors determining theophylline total body clearances. The NYBAID statistical computer program was used to seek the order, priority, and combinations of independent variables (Table I) that correlate with theophylline clearances. Each partition represents a statistical difference of $p < 0.01$, and the circles list the number of subjects (circled), descriptive factor, group mean, and standard deviation (in parentheses).

Such a depiction should be sufficiently frightening to stimulate anyone prescribing theophylline to use measured serum concentrations.

As noted above, theophylline is a good example of a drug for which a good correlation has been shown between serum concentrations and response, both efficacious and toxic.

Figure 35 shows data generated by Mitenko and Ogilvie in which the improvement in FEV_1 in individual patients correlates directly to the serum theophylline concentration.

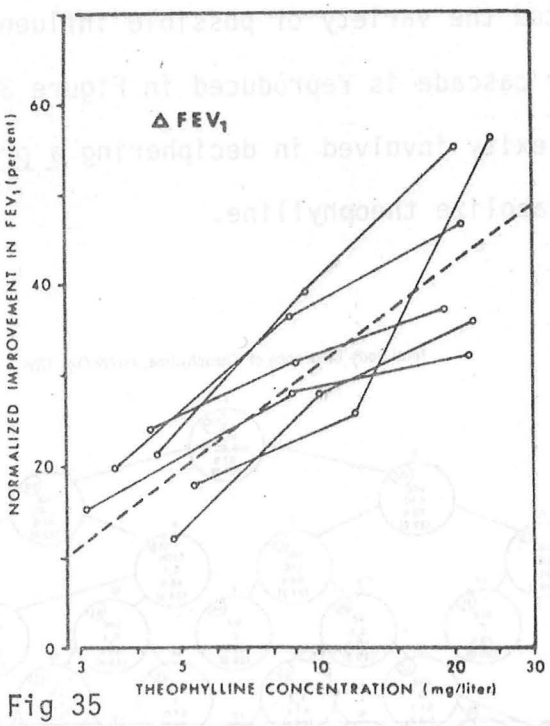


Fig 35

Dose-Response Relation for Changes in Forced Expiratory Volume in the First Second (ΔFEV_1) against the Plasma Theophylline Concentration Plotted Semilogarithmically. Plots for each subject are presented individually (o——o——o), as well as the unweighted least squares regression line for the whole group (----). For each subject the ΔFEV_1 is normalized by division of the mean difference from the placebo value at each drug concentration plateau by the predicted value minus the placebo value.

Similarly, Hendeles et al have demonstrated the direct relationship between serum theophylline concentrations and toxicity (Figure 36).

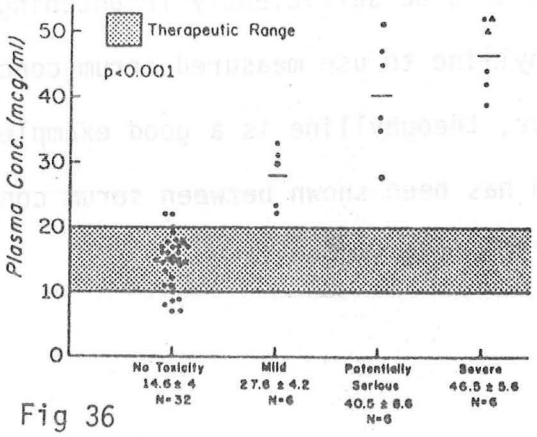


Fig 36

Toxicity Related to Plasma Concentration
* patients who received an excessive dose
▲ patients who received intermittent IV infusions

Similar results have been generated by Zwillich et al (Figure 37).

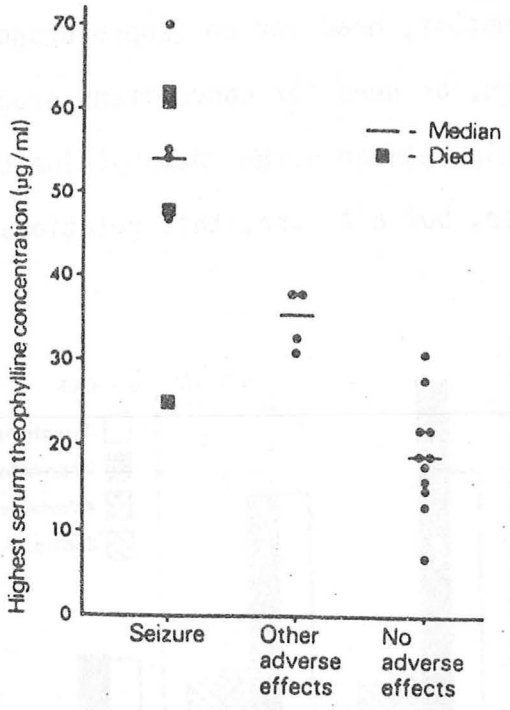


Fig 37: Relationship between serum theophylline concentration and toxicity.

Some authors have questioned whether chronic therapy with theophylline is of benefit to asthmatic patients who are receiving combination therapy.

Figure 38 depicts data generated by Weinberger and Bronsky demonstrating that increasing concentrations of theophylline within the therapeutic range decreased symptoms, need for an isoproterenol nebulizer, need for adrenaline injection, or need for concomitant drugs, supporting not only the good relationship between serum theophylline concentration and efficacious response, but also that this relationship is maintained with chronic therapy.

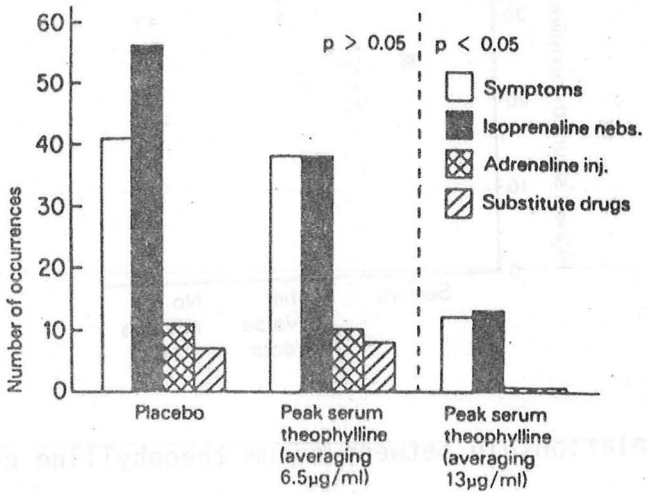


Fig 38: Efficacy of chronic therapy with theophylline related to serum concentration

Again, then, with theophylline it is clear that serum concentration relates better to response than does dose, justifying and fulfilling one of the criteria for utility of measuring serum theophylline concentrations.

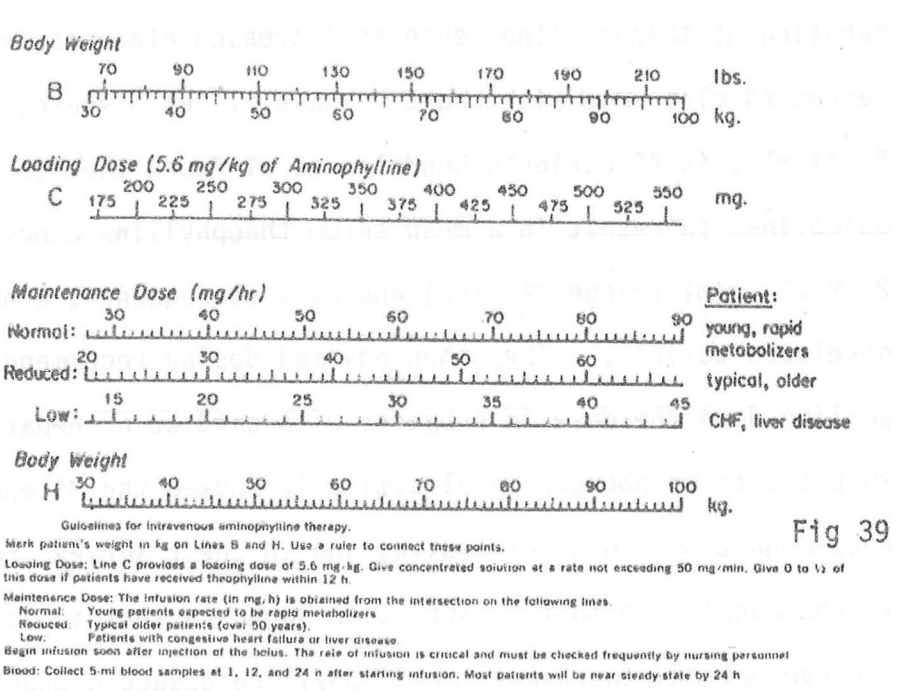
Use of Serum Concentrations as Feedback to Attain Desired Target Concentrations

In 1973, Mitenko and Ogilvie published dosage recommendations to achieve a target serum concentration of theophylline between 10 and 20 µg/ml. To do so, they advised a loading dose of 5.6 mg/kg of amino-

phylline followed by a continuous intravenous infusion at a rate of 0.9 mg/kg/hr. They noted that in their patients this regimen would result in a theophylline concentration of approximately 10 µg/ml in 95% of patients. Many investigators then implemented these recommendations and found considerably different results. For example, Powell et al in 31 normal subjects and 26 patients demonstrated that the Mitenko and Ogilvie recommendations were too high. These authors were also able to demonstrate that a variety of patient demographic factors influenced the handling of theophylline, such as increased clearance with smoking and decreased clearance with heart disease, liver disease, or cor pulmonale. Similarly, in 48 patients Hendeles et al found the Mitenko and Ogilvie guidelines to result in a mean serum theophylline concentration of 21.9±12 µg/ml (range of 7-52) and as a consequence, a number of patients developed toxicity. They then advised dosing recommendations based on scaling down the dose in subjects with cardiac or hepatic disease. In 29 patients Weinberger et al similarly showed the Mitenko and Ogilvie recommendations to be excessive, and in their survey, these authors came to the conclusion that "observation suggests that it is not possible to achieve optimal therapeutic aminophylline dosage without monitoring serum theophylline concentrations". Jenne et al assessed 83 patients receiving 200-300 mg of theophylline every 6 hours by mouth in accordance with the Mitenko and Ogilvie guidelines. They measured trough serum theophylline concentrations in these patients and found a range from 2.9-32.6 µg/ml with a considerable incidence of toxicity among their patients. And lastly, Jacobs et al in 47 patients found a poor relationship between dose and serum theophylline concentration and a good correlation between serum concentration and response with the

Mitenko and Ogilvie recommendations resulting overall in excessive serum concentrations.

With this flurry of papers, it became readily apparent that a variety of patient demographic factors influenced handling of theophylline. Jusko's group attempted to address these problems by quantifying handling of theophylline in 72 patients of different age, body size, cardiac and liver status. From these data, they published the nomogram shown in Figure 39.



Guidelines for intravenous aminophylline therapy.

Mark patient's weight in kg on Lines B and H. Use a ruler to connect these points.

Loading Dose: Line C provides a loading dose of 5.6 mg/kg. Give concentrated solution at a rate not exceeding 50 mg/min. Give 0 to ½ of this dose if patients have received theophylline within 12 h.

Maintenance Dose: The infusion rate (in mg/h) is obtained from the intersection on the following lines.
Normal: Young patients expected to be rapid metabolizers.
Reduced: Typical older patients (over 50 years).
Low: Patients with congestive heart failure or liver disease.

Begin infusion soon after injection of the bolus. The rate of infusion is critical and must be checked frequently by nursing personnel.

Blood: Collect 5-ml blood samples at 1, 12, and 24 h after starting infusion. Most patients will be near steady-state by 24 h.

Fig 39

As is evident, this nomogram predicts the dose needed to achieve a target serum concentration according to age, weight, and presence of cardiac and/or hepatic disease. Evaluation of this nomogram demonstrated attainment of serum theophylline concentrations between 8 and 20 µg/ml in 72% of patients which, at the time was considered to be a success. The inability of this or other such nomograms to more accurately predict needed doses of theophylline is undoubtedly the

result of the many factors which can influence handling of theophylline as the Jusko group subsequently summarized (shown previously in Figure 34). Pancorbo et al assessed the accuracy of the Jusko nomogram in 55 patients, 32 of whom had cardiac or hepatic disease. They found that the nomogram only attained therapuetic serum concentrations (10-20 μg/ml) in 69% of patients. Individualizing therapy, however, by using the Sawchuck method (referred to previously in which 3 separate serum samples are obtained for determination of theophylline concentrations to allow calculation of the individual's handling of theophylline) resulted in attainment of 85% of serum concentrations within the therapeutic range. This assessment of pharmacokinetic parameters in these individual patients revealed a similar situation to that described previously for aminoglycoside antibiotics. Namely, tremendous variability occurs in derived kinetic parameters for theophylline in a population of patients. For example, half-life ranged from 2.5-34.6 hrs, clearance from 0.013-0.185 liters/kg/hr, and volume of distribution from 1.12-1.78 liters/kg. The Jusko nomogram and prior predictive algorithms had all made the fallacious assumption that volume of distribution is constant among patients (Jusko presumed it to be 0.45 liters/kg). With such a false assumption it is no surprise that predictions were erroneous.

Despite these facts, the Food and Drug Administration took it upon themselves to publish guidelines for aminophylline dosing. The motivation for such guidelines was the considerable difficulty occurring in dosing of theophylline in patients with different demographic characteristics. The FDA did not really make any recommendations that had not already appeared in the literature, and unfortunately, by putting their label on a set of recommendations, they most likely gave their recipe

undue credibility. The FDA guidelines have been compared to other methods for individualizing therapy and, as one might have predicted from a predictive algorithm, the results have been poor. The current FDA recommendations are shown in Figure 40 for your interest.

FDA GUIDELINES FOR AMINOPHYLLINE DOSING
(FDA Drug Bull, 1980)

	Loading Dose (mg/kg*)	Maintenance Dose (mg/kg*/hr) Next 12 Hrs	Beyond 12 hrs
Children			
6 mos-9 yr	6	1.2	1.0
9-16 yr and young adult smokers	6	1.0	0.8
Adults			
Healthy, non-smoking	6	0.7	0.5
Older, and those with cor pulmonale	6	0.6	0.3
CHF or liver disease	6	0.5	0.1 - 0.2

*Lean body weight

Fig 40

Just as with any predictive algorithm they serve as a decent starting point in therapy but should not be considered to be sufficient for chronic dosing.

It is interesting to note that one source of error in the FDA guidelines is their use of lean body weight for dosing of theophylline (as did Jusko). While it was noted in previous discussions that lean body weight facilitates the accuracy of dosing with aminoglycoside antibiotics, theophylline has a finite distribution space in fatty tissue, and, as a consequence, one most likely can dose more accurately if distribution into tissues in excess of lean body weight is considered. Data from Lenert et al indicate that the volume of distribution of theophylline is better approximated as 0.5 times lean body weight plus 0.25 times actual weight less lean body weight. Heretofore, most authors have considered the volume of distribution to be 0.44-0.50 liters/kg of lean body weight. This assumption is erroneous as is assuming lack of variability among individuals.

It should, therefore, be no surprise that predictive algorithms have proved unsatisfactory in dosing of theophylline. Do methods to individualize therapy using feedback from serum concentrations perform any better? In 42 patients, McGory and Matzke compared the method of Koup (in which one serum concentration is obtained at a finite time after a test dose and which can theoretically be related to the desired maintenance dose for achieving a target serum theophylline concentration) to the method of Sawchuk in which 3 timed samples after administration of a dose of theophylline are measured with determination of the individual patient's pharmacokinetic parameters. The method of Sawchuk proved to be quite accurate while with the Koup method, the predicted dose varied from the actual dose needed to attain the desired serum concentration by -53.9 to 223.9%. The Sawchuk method proved to be more accurate than predictive algorithms and was also clearly superior to the Koup method. Unfortunatley, the former requires obtaining 3 serum samples in each patient. In 19 patients, Anderson et al assessed the FDA published guidelines, a different Koup method using a hand-held calculator and 2 serum concentrations, and the method of Chiou also using 2 measured serum concentrations. Both the latter methods have the inherent flaw of assuming a constant volume of distribution of 0.44 L/kg. The FDA guidelines achieved subtherapeutic concentrations in all patients and, therefore, were exceedingly inaccurate, as one might presume from a predictive algorithm. The other 2 methods were comparable, with correlations of actual to predicted serum concentrations of approximately 0.86 and with estimation errors ranging from -100 to 46.1%. As noted above, this inaccuracy, though better than the predictive algorithm is probably a function of both methods having assumed volume of distribution to be constant.

Vozeh et al examined 15 acutely ill asthmatic patients including 4 with congestive heart failure, and 2 with hepatic disease. Using a predictive algorithm based on patient demographic factors such as disease, age, smoking, etc., the authors attempted to obtain serum concentrations of 15 µg/ml in all patients. In contrast, as shown in Table 8, they achieved a mean concentration of 18.4 µg/ml with a standard deviation of 15.3.

TABLE 8

IMPROVEMENT IN THEOPHYLLINE THERAPY BY MEASURED CONCENTRATIONS AND METHOD OF CHIOU

(Eur J Clin Pharmacol 18:473-477, 1980)

	Measured Concentrations (µg/ml)		Predicted Concentration (µg/ml)
	Mean ± SD	95% Confidence Interval	
No Feedback	18.4 ± 15.3	4.5 - 49.7 6.0 - 33.0* 5.2 - 43.6*	15
Feedback	14.9 ± 4.8	13.0 - 19.8	14.7 ± 5.1

*Compiled literature sources

The 95% confidence interval for serum concentrations obtained was 4.5-49.7 µg/ml using the predictive algorithm. This lack of accuracy is clearly unacceptable in clinical settings. To verify the findings of their study, these authors also compiled 95% confidence intervals for serum concentrations achieved by predictive algorithms from other literature sources and found them to be quite consistent with those in their own study as shown in Table 8. Using the method of Chiou in these same patients, the authors achieved considerably better results. For a predicted concentration of 14.7±5.1 µg/ml, they achieved 14.9±4.8 with a 95% confidence interval of 13.0-19.8, well within the "therapeutic range".

Mungall et al performed a similar analysis in 15 patients using 2 serum theophylline concentrations for feedback to individualize therapy.

An empirical predictive algorithm resulted in a 95% confidence interval of 3.3-28.5 µg/ml and only 7 of the 15 patients achieved serum theophylline concentrations in the therapeutic range. In contrast, the method using feedback from measured serum concentrations achieved a 95% confidence interval of 10.6-18.2 µg/ml with all patients achieving concentrations in the therapeutic range.

The Bayesian approach of Sheiner has also been assessed with theophylline therapy. Coleman and Hedberg evaluated 3 different approaches in 10 patients, 1 of which was the Bayesian method, and the 2 others of which were similar to that employed by Sawchuk. In this small sample size, they detected no difference among the 3 methods though they did verify that having one measured concentration for feedback improved the estimation of patient handling of theophylline by 60%, again supporting the contention that measured concentrations improved therapy compared to using predictive algorithms alone. In a larger study assessing theophylline therapy in 100 patients, the Bayesian approach was compared to that of Koup and that of Chiou, and was shown to provide considerably better estimates of the individual patient's handling of theophylline.

Most of the foregoing have assessed use of serum concentrations for modification of maintenance doses. Weinberger et al have also addressed this question in terms of the loading dose of theophylline, particularly in those patients who present for therapy and who have received theophylline as out-patients. Clearly, calculation of an appropriate loading dose in this situation requires either measuring or estimating the residual concentration of theophylline in the individual patient.

As shown in Figure 41, if a loading dose was superimposed on a "guestimate" of the residual serum concentration, very few patients attained concentrations within the therapeutic range and toxicity became a problem. On the other hand, as shown on the right side of the figure, if loading doses were guided by measured residual serum concentrations, considerably more patients achieved serum concentrations within the therapeutic range.

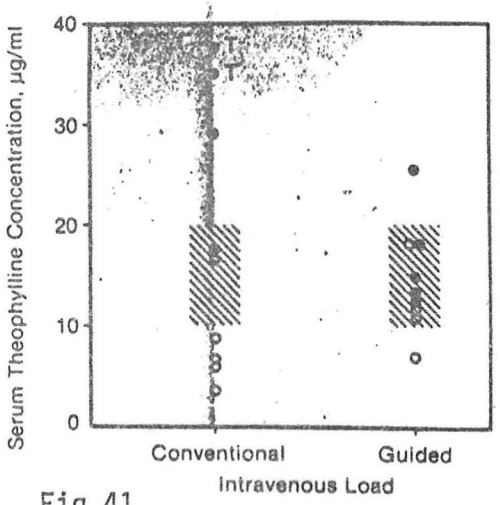


Fig 41
Serum theophylline concentrations resulting from conventional loading doses of aminophylline and from doses based on initial drug concentration. Open circles indicate children; closed circles, adults; T, theophylline toxicity; shaded area, therapeutic range.

In summary, measurements of serum theophylline concentrations used as feedback for individualizing therapy improved the ability to achieve a target serum concentration within the therapeutic range. Of the variety of techniques available to do so, it appears that the Bayesian approach is the most accurate. In addition, this approach can utilize information from one serum level, in contrast, for example, to the method of Sawchuk which requires three or with the method of Chiou which requires two, and it does not require what is usually the fallacious

assumption that one of the kinetic parameters such as volume of distribution is constant.

Cost-Effectiveness of Monitoring Serum Drug Concentration

Because of the very good correlations of serum concentrations of theophylline to both efficacious and toxic response, one would presume that using serum concentration measurements to attain the desired concentration within an individual patient would prove cost effective. Unfortunately, no data address this point. To fill this gap, it is our goal to perform such a study and we, in fact, have submitted protocols to the Institutional Review Board at both Southwestern Medical School and the VA Hospital to assess the cost-effectiveness of using serum theophylline concentrations to individualize therapy. We feel that such assessment requires quantifying such end-points as decrease in toxicity, but also measures of efficacy such as hospitalization time, return rate to the emergency room, duration of stay in the emergency room, need for concomitant medications, etc. Hopefully, many in the audience will have a chance to facilitate our seeing this study to fruition.

In summary, then, a number of drugs meet the criteria listed in Table 1 for defining utility of measuring serum drug concentrations. With the drugs presented in the preceeding section, the serum concentration clearly correlates better to response than does dose. In addition, feedback from serum drug concentration values clearly allows better attainment of desired concentrations and response than do predictive algorithms based on population derived data estimating handling of drugs as a function of the demographic characteristics of the patient. Lastly, though data tend to be sketchy, it appears that using serum drug concentrations is cost-effective. Unquestionably, the toxicity due to

digitalis glycosides is decreased, and there is one clear-cut study demonstrating the cost-efficacy of individualized aminoglycoside therapy in burn patients. This area of cost-effectiveness is clearly in need of further documentation; however, it is not unreasonable to assume that using measures of drug concentration improves the quality of patient care. Costs sufficient to outweigh this benefit are not obvious and would be unexpected. It is important to emphasize that data similar to those discussed with aminoglycosides, digoxin, phenytoin, and theophylline also exist for other drugs. Clearly, other antiepileptics, other antiarrythmic agents, methotrexate etc. can be used more effectively by using measured serum drug concentrations. Overall, the data are such that the onus must be placed on nonusers of serum drug concentrations to justify an approach to therapy which appears from the data to be suboptimal.

METHODS FOR INDIVIDUALIZING THERAPY USING MEASURED SERUM DRUG CONCENTRATIONS--AN ARGUMENT FOR THE USE OF COMPUTERS

In the preceeding sections dealing with the demonstration that use of serum concentrations to individualize therapy was more efficacious than predictive algorithms, a variety of methods for implementing such a feedback loop were presented with no discussion of the methodolgy involved. A collation of the preceeding discussion was that all methods using feedback from measured serum concentrations improve the ability to achieve a target concentration with any of the drugs discussed. Of the various methods compared, that of Sawchuk and the Bayesian approach were most accurate. In this section of the discussion, I will present some of these various methods with one of my main goals to emphasize that the mathematics involved are complex, but are readily adaptable to a computer.

Though hand held calculator and graphical methods have been promulgated at various times, these tend to be exceedingly tedious and less than state-of-the-art. It seems that in many walks of life the wave of the future is computers. Therapeutics appears to be no exception.

Chiou Method of Predicting Individual Pharmacokinetics

The Chiou method uses two samples obtained during a maintenance infusion. As shown in Figure 42, these values and the known infusion rate plus the time interval between the 2 samples can be used to calculate the individual subject's clearance if a value for volume of distribution based on population data is assumed.

CHIOU METHOD OF PREDICTING INDIVIDUAL PHARMACOKINETICS

During a continuous intravenous infusion, without having given a loading dose, obtain 2 samples during the ascent, preferably 4 Hr apart
Then,

$$\text{Clearance} = \frac{2K_o}{Cp_1 + Cp_2} + \frac{2V_d(Cp_1 - Cp_2)}{\Delta t(Cp_1 + Cp_2)}$$

Where, K_o = infusion rate
Cp_1 and Cp_2 = measured concentrations
V_d = volume of distribution
(assumed to be constant)
Δt = elapsed time between Cp_1 and Cp_2

Then

$$\text{Maintenance infusion rate} = Cp_{ss} \text{ (desired)} \times \text{Clearance}$$

Fig 42

A desired serum maintenance infusion rate can then be calculated based on the target concentration to be attained and the individual's clearance as calculated by the Chiou method. As noted in the previous discussion, this method is accurate but requires 2 samples that must be obtained during a continuous infusion and, therefore, might not be appropriate for all drugs. The major liability, however, is its assumption of a volume of distribution based on population based pharmacokinetics rather

than having the ability to calculate the individual patient's volume of distribution. As pointed out in the previous discussion, particularly with theophylline and aminoglycoside antibiotics, volume of distribution varies at least 10 fold when quantified in large patient groups; assigning an inflexible value to this kinetic parameter is hazardous.

Koup Method of Predicting Individual Pharmacokinetics

The Koup method obtains one sample 6 hours after the intravenous administration of a test dose. The concentration of a sample obtained at 6 hours, then, is a function of the equation shown in Figure 43.

KOUP METHOD OF PREDICTING INDIVIDUAL PHARMACOKINETICS

Administer a test dose by intravenous infusion and obtain one sample 6 hrs after the start of the infusion.

Then,

$$\text{Concentration at 6 Hr} = \frac{\text{Dose}}{V_d k_d T}(1-e^{-k_d T})e^{-k_d(6-T)}$$

Where, V_d = volume of distribution (assumed to be constant)

k_d = elimination rate constant

T = duration of infusion

Solve for k_d

Then,

$$\text{Maintenance infusion rate} = Cp_{ss} \times k_d V_d \text{ (desired)}$$

Fig 43

In this equation, the duration of infusion and dose are known, and if volume of distribution is approximated by a population based value assumed to be constant, the elimination rate constant can be derived. Then the maintenance infusion needed to obtain a desired concentration at steady state can be easily calculated using values of the elimination rate constant derived from the above equation and the population based volume of distribution. Similar to the method of Chiou, the Koup method

is accurate and has the advantage of requiring only one serum determination. Its disadvantages are that the sample must be obtained exactly 6 hours after the infusion, the erroneous assumption that the volume of distribution of a particular drug is constant in all patients, and, in addition, this method becomes considerably less accurate in patients in whom the half-life of the drug for which it is being utilized is > 8-10 hours. With theophylline, for example, this liability would preclude the utility of the Koup method in many patients with congestive heart failure or hepatic disease, the very patients in whom individualizing therapy is most important.

Sawchuk Method of Predicting Individual Pharmacokinetics

Using the Sawchuk method requires obtaining 3 serum drug concentrations after an infused dose. One attempts to attain these soon after the infusion ends, at or near the trough, and somewhere in between. From these 3 points a linear least squares regression fit of the natural logarithm of the serum concentration versus time results in a straight line, the negative slope of which is the elimination rate constant. From the equation of the line, a maximum concentration can be extrapolated as can a minimum or trough concentration.

Since the infusion rate and the duration of the infusion are known, volume of distribution can be calculated for the individual patient as shown in Figure 44.

SAWCHUK METHOD OF PREDICTING INDIVIDUAL PHARMACOKINETICS

After an infused dose, obtain 3 samples

Perform a linear least squares fit of ln Cp versus time,

Then, calculate the individual's V_d:

$$V_d = \left(\frac{K_o}{k_d}\right) \frac{1-e^{-k_d T}}{Cp_{max} - (Cp_{min} e^{-k_d T})}$$

Where, K_o = infusion rate

k_d = elimination rate constant, the negative slope of the line

Cp_{max} = concentration at the end of the infusion, the extrapolated Y-intercept of the line

Cp_{min} = trough concentration, extrapolated from the line

T = duration of infusion

Then, calculate the dosing interval, τ, necessary to achieve the desired Cp_{max} (peak) and Cp_{min} (trough) concentrations:

$$\tau = -\frac{\ln \frac{Cp_{min}}{Cp_{max}}}{k_d} + T$$

Then, calculate dose as

Dose $= K_o T$

Where,

$$K_o = k_d V_d Cp_{max} \frac{(1-e^{-k_d \tau})}{(1-e^{-k_d T})}$$

Fig 44

Then, the clinician can select a desired maximum and minimum, i.e., peak and trough concentration, and calculate the dosing interval necessary for this swing from peak to trough knowing the elimination rate constant and the duration of the infusion. Finally, the desired infusion rate of drug can be calculated knowing the elimination rate constant and volume of distribution, the desired maximum concentration and the frequency with which it will be administered. The Sawchuk method is quite accurate and can calculate both the individual's volume of distribution as well

as clearance and elimination rate constant in direct contrast to the methods of Chiou and Koup. Its main drawback is the necessity for 3 samples and the mathematical complexity relative to the other 2 methods.

Bayesian Method for Individualizing Drug Therapy

As noted in the first section of this discussion presenting data on individual drugs, use of the Bayesian approach when tested against other methods always proved to be the most accurate. This method has been developed by Sheiner and colleagues and was utilized by them because of their belief that interindividual variability affected all kinetic parameters and, consequently, the only approach that could be expected to work most optimally would be one having the flexibility of changing all relevant parameters. A Bayesian approach is particularly appropriate for this kind of situation, for it allows modification of all parameters based on their inherent variability observed in the population. For example, if population based studies demonstrate for a certain drug that the clearance value has a large standard deviation, i.e., much variability in the population, whereas the volume of distribution has a small standard deviation and, therefore, shows little variability, the Bayesian approach will allow weighting such that if an individual behaves differently from the population average (i.e., an observed serum drug concentration differs from that predicted) both volume of distribution and clearance will be changed to accommodate these differences. Clearance will be changed to a greater extent than will volume of distribution because variability in clearance is greater than is variability in volume of distribution. This ability to weight and thereby proportionally change different kinetic parameters is the key feature of the Bayesian approach. Another advantage is that it can

accommodate any number of serum drug concentrations. Its flexibility allows one to weight the obtained serum concentrations rather than considering them all to be of equal importance. For example, a patient's status may be changing with time, and as a consequence, one may place most credence on the most recently obtained serum concentration. The Bayesian approach allows one to use information from previously obtained serum concentrations but to most emphasize the recently obtained samples, just as one would in actual therapeutic decision making.

The drawback of the Bayesian approach is its mathematical complexity as can be appreciated in Figure 45.

ALGORITHM FOR BAYESIAN FEEDBACK

Minimize the Function:

$$\sum_{n=1}^{\text{Number of kinetic parameters}} \frac{(P'_n - P_n)^2}{(SD_n)^2} + \sum_{m=1}^{\text{Number of measured concentrations}} \frac{(Cp'_m - Cp_m)^2}{(SE_m)^2}$$

Where,

Kinetic parameters = volume of distribution
= clearance
= compliance factor
= etc.

P′ = revised parameter estimate

P = population based parameter value

SD = standard deviation of the kinetic parameter

Cp′ = predicted concentration from the revised kinetic parameter estimate

Cp = observed concentration

SE_m = standard deviation of the measurement error

and

$SE = [Cp' (SME) + 0.25] (1.005^t)$

Where,

SME = assay measurement error

t = time since the measured concentration

(this allows the most recent measurement to carry the most weight)

Fig 45

The method minimizes a function consisting of kinetic parameters and measured serum concentrations, comparing population-derived parameters to revised parameter estimates and comparing predicted serum concentrations to observed concentrations. Weighting is accomplished by a technique of using standard deviations in the denominator. Though all previously mentioned methods for individualizing therapy can be accomplished on programmable hand-held calculators (or by hand for the truly inspired), the Bayesian approach clearly requires a computer. On the other hand, its superiority has been clearly demonstrated, as noted in the previous citations, and with other drugs such as lidocaine which have not been discussed in this protocol.

It is my contention that the requirement for a computer should not be considered a drawback, for even though the previous methods can be implemented on less sophisticated equipment, the methods outlined above use the simplist case, in that they do not consider the situation in which a patient has received some form of therapy before the individualization approach is implemented. For example, if a patient has been receiving drug as an out-patient, as he might if he were taking theophylline or digoxin, the residual concentration in that patient at the time of implementation of the individualization strategy must be estimated. To do so requires solving the equation shown in Figure 46.

TO CALCULATE RESIDUAL CONCENTRATION FROM OUTPATIENT DOSING

$$\text{Residual} = \frac{(F)\,(\text{DOSE})\,(k_a)}{V_d\,(k_a - k_d)} \left[\frac{1-e^{-Nk_d\tau}}{1-e^{-k_d\tau}} \left(e^{-k_d t'}\right) - \frac{1-e^{-Nk_a\tau}}{1-e^{-k_a\tau}} \left(e^{-k_a t'}\right) \right]$$

Where, F = fraction of dose absorbed
V_d = volume of distribution
k_a = absorption rate constant
k_d = elimination rate constant
N = number of doses
τ = dosing interval
t' = time from the last dose till the current time

Fig 46

Similarly, if a patient has received in-patient therapy (for example, several doses of an aminoglycoside antibiotic or a loading dose and a maintenance infusion of theophylline) the impact of these doses must be estimated using equations shown in Figure 47.

TO CALCULATE THE CONCENTRATION FROM INPATIENT DOSING

$$\text{Concentration at time, } t = \sum_{n=1}^{m} C(t)_n$$

Where m = the number of inpatient doses

For an oral dose:

$$C(t)_n = \frac{F\,\text{Dose}\,k_a}{V_d(k_a - k_d)}\left(e^{-k_d\Delta t} - e^{-k_a\Delta t}\right)$$

For an intravenous bolus dose:

$$C(t)_n = \frac{\text{Dose}}{V_d}\,e^{-k_d\Delta t}$$

And for an intravenous infusion

$$C(t)_n = \frac{\text{Dose}}{\text{Clearance} \times T}\left(1 - e^{-k_d\Delta t}\right)$$

where, Δt = time since the start of the n^{th} dose

T = duration of infusion

Fig 47

Obviously, these equations are far from trivial and, in and of themselves, could well justify use of a computer for their solving, particularly if these are wed to other individualization strategies. Moreoever, one must also consider that the Bayesian approach is a general approach. In addition to its usefullness for drugs with first order elimination characteristics such as aminoglycosides, digoxin, and theophylline, it can also be used for drugs with dose-dependent elimination such as phenytoin, whereas the other methods outlined above cannot be utilized for the latter drugs. It would seem to make more sense to use a general approach applicable to all agents in our therapeutic armamentarium, than to derive specific approaches for different varieties of drugs.

In conclusion then, many methods can be used to individualize therapy of drugs with narrow therapeutic indices. My bias is to use the Bayesian approach, implemented on either main frame or small computers. I think this is the ideal avenue of pursuit. The facility and utility of this approach can be readily seen with the examples demonstrated during grand rounds. Its applicability to therapeutic settings should be obvious. It is important, however, to also note that there are other uses of measurements of serum drug concentrations, the most important of which are shown in Table 9. These need no amplification and most are obvious, save that which has been addressed today, namely guiding dosage regimen design. Hopefully, through this and other similar presentations, you will become convinced that serum drug concentration determination is a mainstay of therapy, and under-utilization of this approach is tantamount to inappropriate care of your patient.

TABLE 9

USES OF MEASUREMENTS OF SERUM DRUG CONCENTRATIONS

1. Confirmation of attainment of a drug concentration within the "therapeutic" range
2. Supplementary data in suspected drug toxicity
3. To guide dosing regimen design - particularly in clinical conditions in which changes from "average" in drug disposition occur (disease, drug interactions, etc)
4. Drug identification in overdose settings
5. To assess compliance

CAUTIONS REGARDING INAPPROPRIATE USE OF SERUM DRUG CONCENTRATIONS

The power of the techniques for individualizing therapy is critically dependent on the quality of the data utilized and the ability of the physician to adequately interpret their meaning. If a number of simple principles are ignored, no matter how sophisticated the technology, the

utility of serum drug concentrations becomes negligible. In other words, the old axiom holds that "garbage-in yields garbage-out".

The magnitude of this problem can be exemplified by data from several sources shown in Table 10.

TABLE 10

USEFULL(LESS)NESS OF SERUM DRUG CONCENTRATIONS WHEN PHARMACOKINETIC PRINCIPLES ARE IGNORED

Number of Assays	% Useful	Reference
Gentamicin		
212	20	Anderson et al
45	22	Flynn et al
43	14	Bollish et al
Digoxin		
138	22-50	Floyd and Taketomo
100	67	Hladik and DuJovne
116	35	Greenlaw et al
145	64	Slaughter et al

These different investigators assessed interpretability and appropriate utilization of gentamicin and digoxin serum concentration determinations and found the users to be frighteningly naive, if not ignorant, as reflected in the low percent of values that were useful. Misinterpretation of serum drug concentrations is probably more likely to be harmful than helpful, and one must be particularly cognizant of the need to use them appropriately, otherwise all of the foregoing comes to naught. In this vein, Table 11 lists situations in which measuring a serum concentration may not be useful. It is important to review these so that utility can be maximized and cost-effectiveness attained.

TABLE 11

WHEN MEASURING A SERUM DRUG CONCENTRATION MAY NOT BE USEFUL

1. The measurement is inaccurate
2. The concentration correlates poorly with response
3. It is clinically unnecessary
   a. Wide therapeutic index
   b. There is a readily measurable clinical end-point of response
4. Active drug metabolites are not measured
5. The "usual" therapeutic range is altered
6. Pharmacokinetic principles are ignored
   a. Futility of defining peak concentration after oral or intramuscular administration
   b. Sampling during the distribution phase
   c. Ignoring the concept of attainment of steady state
7. Time of dosing and sampling is inacurrate

The responsibility for accuracy of serum drug concentration determinations rests with the Clinical Pathology Laboratory. One should realize that if everything else seems to be "right" in a patient and the value obtained from the laboratory does not seem to "fit", there could possibly be a measurement error. McCormick et al presented interesting data when samples were blindly submitted to different laboratories as an assessment of their quality control. Figure 48 depicts representative data which shows the values for digoxin determined by one laboratory on samples containing 1.8 ng/ml of digoxin.

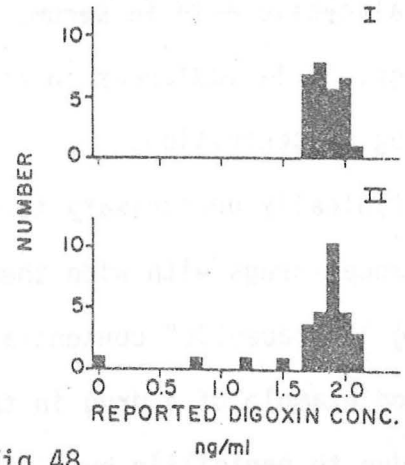


Fig 48
Digoxin Concentrations Reported by Laboratory A for Samples Containing 1.8 Ng per Milliliter Submitted as Designated Quality-Control Specimens (I) or as Simulated Clinical Specimens (II).

The top panel of the slide, which appears to be fairly accurate, represents those samples designated as quality control specimens, whereas the lower panel represents determinations on those samples submitted as clinical specimens. The difference presumably is accounted for by the technical personnel's paying more attention to the handling and assaying of the quality control samples. Overall, the Clinical Pathology laboratories performed well, but one must always realize that measurement of the serum drug concentration itself can be a potential source of error.

Obtaining a serum drug concentration may not be useful for a variety of drugs if the concentration in serum correlates poorly with response. Numerous examples exist, such as phenoxybenzamine which irreversibly blocks adrenergic receptors such that the effect persists long after phenoxybenzamine has been eliminated from serum. Similarly, with administration of aspirin, the acetyl group of acetylsalicylic acid splits off and binds to platelets, irreversibly inhibiting prostaglandin synthetase. Since the platelet cannot generate new enzymes, this effect lasts for the platelet's life span which vastly exceeds the duration of measurable amounts of acetylsalicyclic acid in serum. With such drugs, in many therapeutic settings, it is ludicrous to attempt to interpret much less measure a serum drug concentration.

Often it is clinically unnecessary to measure a serum drug concentration. For instance, drugs with wide therapeutic indices can be used to excess, assuring "therapeutic" concentrations without risking toxicity. Penicillin is a good example of a drug in this category. One occasionally observes toxicity due to penicillin but, other than allergic reactions, extremely high serum concentrations are necessary to cause side effects. Consequently, we usually administer doses of penicillin which are substantial and in terms of efficacy probably represent "overkill". The benefits to be gained by measuring a serum penicillin concentration and more carefully targetting the minimal level that will still be efficacious would clearly not be cost-effective. Another situation in which measuring serum drug concentrations is not clinically necessary is when there is a readily measurable clinical end-point of response. Beta-blockers are good examples of drugs in this category, for clinical assessment of beta-blockade is much easier and less expensive than is a

serum assay for the various beta-blockers. Oral anticoagulants are other good examples, for it is much simpler to measure the prothrombin time than it is to measure the actual concentration of drug.

Because of the variability among patients in the relationship between the serum concentration attained and response, it is unfortunate that with more drugs we cannot readily measure response as opposed to serum concentration. It should be noted that the same approach taken for individualizing therapy using a target serum concentration can be used with drugs with readily measurable endpoints of response, using response as the target. In fact, computer programs have been devised and are being tested which use the Bayesian approach to individually relate dose to response. This serves as yet another example of the potential usefulness of computers to optimize therapeutics.

It becomes exceedingly difficult, if not impossible, to interpret a serum drug concentration if that drug has active metabolites, particularly if they are not measured. Table 12 presents a list of some drugs with active metabolites and quick perusal reveals that for the drugs in this list in which we measure serum drug concentration the metabolite is often ignored.

Table 12

DRUGS WITH ACTIVE METABOLITES

DRUG	METABOLITE
Acebutolol	N-acetylacebutolol
Acetohexamide	Hydroxyhexamide
Allopurinol	Oxypurinol
Amitriptyline	Nortriptyline
Cefotaxime	Desacetylcefotaxime
Chloral hydrate	Trichlorethanol
Chlordiazepoxide	Desmethylchlordiazepoxide
Clofibrate	Parachlorophenoxy-isobutyric acid
Codeine	Morphine
Cyclophosphamide	4-Hydroxycyclophosphamide and aldophosphamide
Cytarabine	Uracil arabinoside
Diazepam	Desmethyldiazepam
Digitoxin	Digoxin
Digoxin	Digoxigenin-mono-digitoxide and Digoxigenin-bis-digitoxide
Flurazepam	Desethyiflurazepam
Glutethimide	4-Hydroxyglutethimide
Imipramine	Desipramine
Meperidine (pethidine)	Normeperidine
Methamphetamine	Amphetamine
Methimazole	3-methyl-2-thiohydantoin
Metoprolol	α-hydroxymetoprolol
Nalidixic acid	7-hydroxynalidixic acid
Pancuronium	3-hydroxypancuronium
Phenacetin	Acetaminophen
Phenylbutazone	Oxyphenbutazone
Prednisone	Prednisolone
Primidone	Phenobarbital
Procainamide	N-acetylprocainamide
Propoxyphene	Norpropoxyphene
Propranolol	4-Hydroxypropranolol
Sodium nitroprusside	Thiocyanate
Sulphonamides	Toxic acetylated metabolites

Even if the metabolite is measured and reported to the clinician, however, as is the case with procainamide and N-acetylprocainamide, interpretability of this value is not assured. At one time clinicians took the simplistic approach of simply adding the procainamide and N-acetylprocainamide concentrations and aimed for a therapeutic range accordingly. Clearly, this is unacceptable, for the metabolite has a different spectrum of activity than the parent drug, and basically we do not know how to interpret serum concentrations of N-acetylprocainamide. A similar problem occurs with quinidine. The therapeutic range that has been defined for quinidine used nonspecific assay methods which included measurements of metabolites with lesser activity than the parent compound. Guentert et al have clearly shown that use of specific assays for quinidine results in a "therapeutic range" of considerably smaller values of quinidine than those used previously. Studies are now needed to define the therapeutic range for quinidine using the specific assays that most clinical laboratories can now implement or have now implemented. In situations such as those mentioned above, it becomes exceedingly important to focus more on clinical endpoints of response than on actual measures of serum drug concentration. In fact, in many instances it may potentially be more harmful to obtain such measurements, and one's patient would be best served if the drug concentration were not determined at all.

When most clinical laboratories report the value for the drug measured in the patient's sample, they include a "normal therapeutic range". In some situations, however, the therapeutic range must be redefined. Phenytoin is the prototypic example. Phenytoin is tightly bound to serum proteins, and it is the amount of free drug which is

available to the site of action and responsible for pharmacologic effect. However, it is the total amount of phenytoin in blood which is measured by the clinical laboratory. If a change in binding occurs, as may happen in drug interactions, in patients with hypoalbuminemia, or in patients with uremia the "usual" therapeutic range must be redefined. This phenomenon is illustrated schematically in Figure 49.

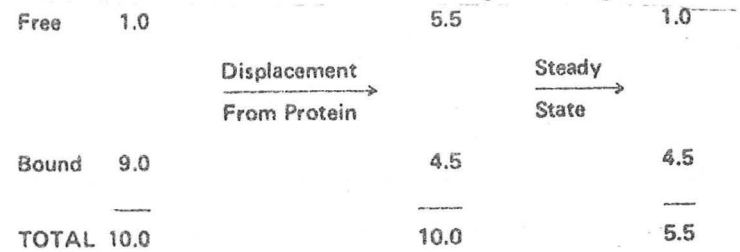


Fig 49: Schematic illustration of the effect of altered protein binding on concentrations of phenytoin.

In the "normal patient" 90% of phenytoin is bound so that if a total serum concentration of 10 µg/ml was reported from the laboratory, this value would represent 1 µg/ml free in plasma and 9 µg/ml bound to serum proteins. If instantaneous displacement from protein occurred (obviously not the case clinically and for illustrative purposes only) the free concentration of phenytoin would increase with a concomitant increase in pharmacological effect most likely resulting in toxicity if the patient had been previously in the therapeutic range. However, this increased free concentration is not only available to the site of action, but it can also distribute into tissues where activity does not occur (for phenytoin most likely adipose tissue). A new steady-state is achieved where the free concentration of drug is identical to that previously, though the % bound is less and the total serum concentration reported from the clinical laboratory is less. As a consequence, in the clinical situation represented by the right side of the schematic, a total serum

concentration of 5.5 µg/ml results in an identical pharmacological effect to the total serum concentration of 10 µg/ml shown on the left side of the schematic. Therefore, if the laboratory reports total serum concentrations in such clinical situations, the "therapeutic range" must be redefined. The consequence of not redefining the therapeutic range is as if the patient on the right side of the schematic was still suffering seizures. The physician, after receiving the laboratory result of of 5.5 µg/ml might inappropriately presume that the patient was at a subtherapeutic dose of phenytoin, increase the dose, and cause toxicity. Reidenberg and Affrime have attempted to redefine the therapeutic range of phenytoin in patients with uremia as shown in Figure 50.

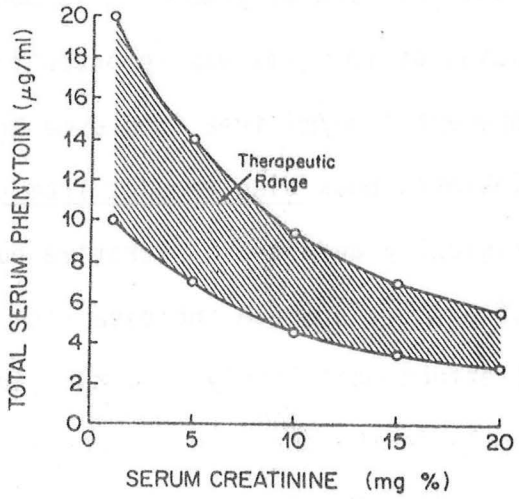


Fig 50: Redefined "therapeutic" range of phenytoin relative to renal function.

This figure demonstrates the principles discussed, though it is a poor representation, because serum creatinine is obviously an inadequate index of renal function across all ages of patients. One should not use values from such a curve with too much faith. They should mainly make one cautious in those situations in which phentyoin may be displaced

from serum proteins, i.e., uremia, hypoalbuminemia, and drug interactions in which displacement from protein occurs.

An illustration of this same phenomenon in nephrotic patients with hypoalbuminimia is shown in Table 13.

TABLE 13

EFFECT OF HYPOALBUMENEMIA ON PHENYTOIN
(J Clin Invest 55:1182-1189, 1975)

	Controls	Nephrotic Syndrome
Total Serum Concentration (μg/ml)	6.8	2.9
Protein Bound (%)	89.9	80.8
Unbound Fraction (%)	10.1	19.2
Volume of Distribution (L/Kg)	0.3	0.59
Concentration of Unbound Drug (μg/ml)	0.69	0.59
Volume of Distribution of Free Drug (L/Kg)	2.69	3.4

The same phenomenon as illustrated in uremia occurs; namely, total serum concentration is halved as the amount bound to serum proteins decreases from 90 to 80% with a concomitant doubling of the fraction unbound from 10 to 20%. This increased free drug can distribute to nonactive sites, doubling the volume of distribution such that the concentration of unbound drug is virtually identical in patients with the nephrotic syndrome compared to control subjects. Other drugs in which this identical phenomenon occurs include valproate and coumadin. With coumadin the problem of interpretation is avoided because clinical effect rather than serum concentration is measured. A redefinition of the therapeutic range of phenytoin or any other drug does not obviate the usefulness of serum drug concentrations in individualizing therapy. One must, however, be particularly cognizant of the ramifications of the target serum concentration he wishes to achieve in his individual patient.

Perhaps the most common setting in which measuring serum drug concentrations may not be useful is when pharmacokinetic principles are ignored, a circumstance which is entirely avoidable. A frequent source of error of this type is when the clinician obtains a "peak" serum concentration after having administered a drug by mouth or intramuscularly. It is absolutely impossible to predict a priori at which time a peak concentration will occur in an individual patient. Unless a series of samples are gathered, one cannot know if the sample is obtained on the upslope, at the peak, or on the downslope of the serum concentration versus time curve. This fact is illustrated in Figure 51 which is a schematic of 3 curves all having the same area under the curve, (in other words, bioavailability of the preparation is the same for all 3 curves) and the same elimination half-life.

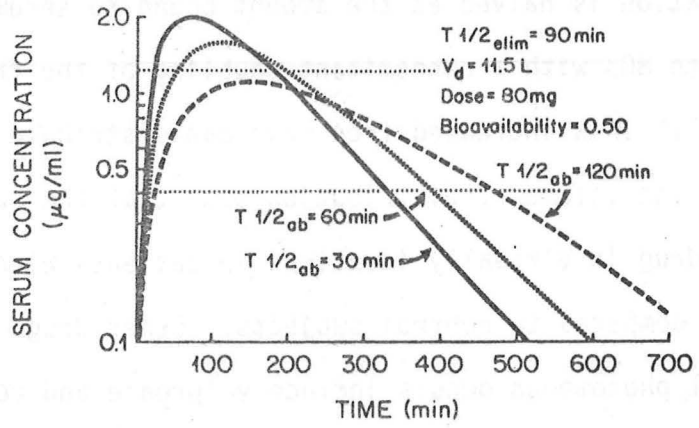


Fig 51: Idealized absorption profile curves where only the rate of absorption differs.

The only difference in these 3 curves is the rate of absorption. Again, it is absolutely impossible to predict a priori on which curve an individual patient would fall. In addition, patients may have variability in the lag time before which drug begins to be absorbed, further com-

plicating the issue. If one has administered a drug by mouth or intramuscularly it is best to attempt to avoid obtaining a serum drug concentration during the absorption phase. This can best be avoided by obtaining a trough concentration or a sample on the downward slope of the elimination phase.

Another frequent source of error from ignoring pharmacokinetic principles is obtaining a serum drug concentration during the distribution phase of the drug. This most often occurs after intravenous administration of a drug by either infusion, but particularly by intravenous bolus. Different drugs equilibrate at different rates with tissues, and it is that drug reaching the tissue which is active. Consequently, before equilibration is achieved, very high serum concentrations may be associated with very low concentrations at the active site and little pharmacological effect. In contrast, after sufficient time has elapsed, the serum concentration may have decreased while the concentration in tissues has increased. During this dynamic phase of equilibration with tissue (actually pseudoequilibration since equilibration can never completely occur unless the patient is at steady-state with a continuous intravenous infusion) the serum concentration cannot be appropriately interpreted.

This phenomenon is illustrated in Figure 52 which demonstrates the relationship between the plasma procainamide concentration and response monitored as a change in the QT interval.

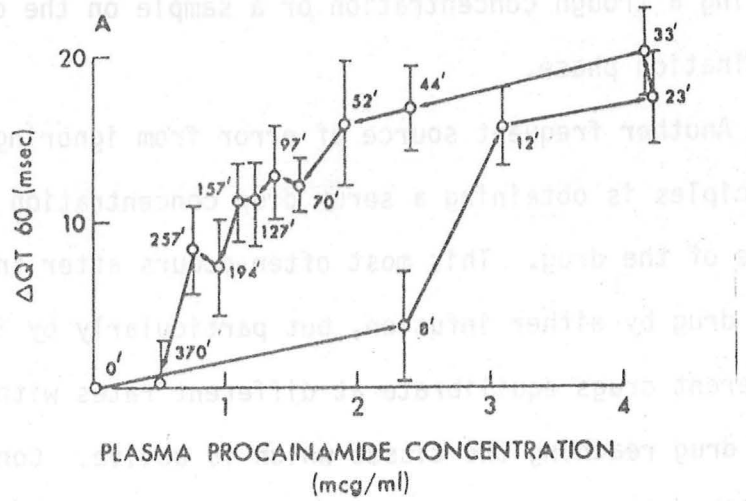


Fig 52: Relationship between plasma procainamide concentration and response at different sampling times after an intravenous infusion.

This depiction shows a hysteresis loop in which, during the initial blood sampling, there is clearly a dissociation between concentrations in blood and clinical response. For example, at 8 minutes the plasma concentration of approximately 2.3 µg/ml is associated with only approximately a 4 millisecond change in the QT interval, whereas at 44 minutes a virtually identical plasma procainamide concentration is associated with a change in QT interval of approximately 17 milliseconds. This latter value is after distribution has ceased and is at a time in which a plasma procainamide concentration can be validly interpreted. It is important to avoid sampling of any drug during the distribution phase.

This can be accomplished with most drugs after an intravenous bolus dose or an intravenous infusion, if an interval of at least 30 minutes, or preferably 60 minutes, occurs before sampling is performed. The exception to this rule is digoxin which has a prolonged distribution phase lasting 6-8 hours. Consequently, samples for determination of serum digoxin concentration should not be obtained any sooner than 8 hours after administration of the drug; so doing renders them uninterpretable.

A last common situation in which pharmacokinetic principles are ignored is the clinician's inattention to the concept of attainment of steady-state. For any drug, the time necessary to reach steady-state equals 4 to 5 times the serum half-life. Though the half-life of the drug is difficult to estimate in individual patients, one can usually guestimate an appropriate "ball park" figure. If one samples at an assumed steady-state though steady-state has not yet been reached, misinterpretation and inappropriate clinical responses are likely to occur. This scenario is illustrated in Figure 53.

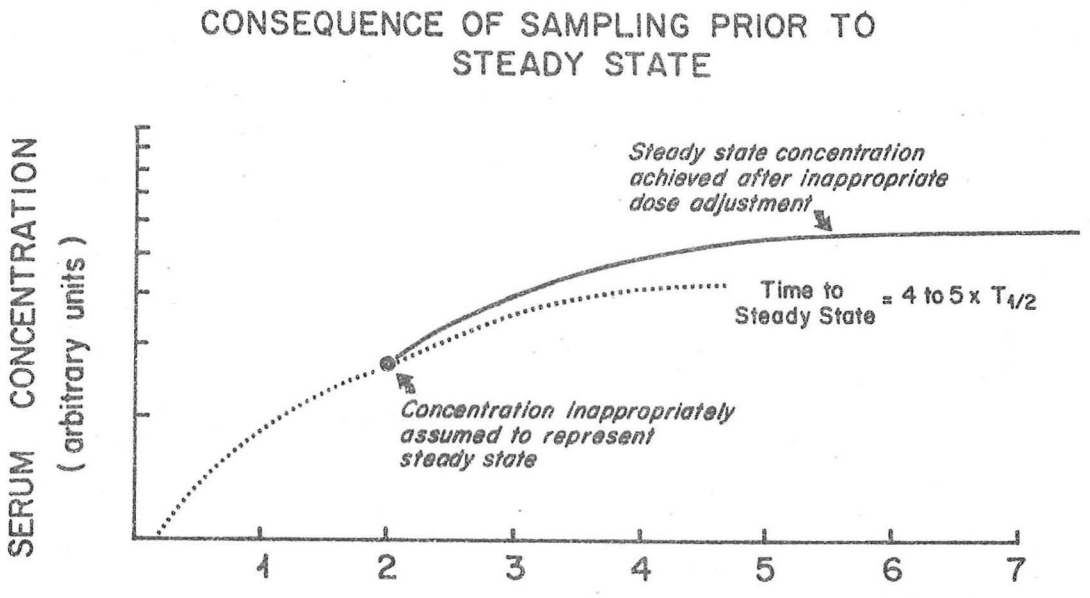


Fig 53

The dashed curve is an idealized representation of the attainment of steady-state of a drug after approximately 4 to 5 half-lives. In this example the steady-state concentration is approximately 4. If a sample were obtained after 2 half-lives, the value would be approximately 2.7. If the clinician inappropriately assumed this to represent steady-state and his target concentration were 4, he would increase the dose. After an increase in dose, it again takes 4 to 5 times the serum half-life to reach the new steady-state, and as depicted in this figure by the idealized solid line, the patient, after inappropriate dose adjustment would reach a serum concentration of approximately 6 which could well be in the toxic range. If the clinician is not certain where he is in relationship to steady-state, he should obtain 2 separate serum concentrations to assess whether the concentration is still increasing (or if the dose has been adjusted downward, decreasing). Otherwise, interpretation of the serum concentration becomes exceedingly difficult and can be misleading.

The pharmacokinetic principles illustrated above are not difficult, and the fact that they are frequently ignored is inexcusable. A few simple rules when disobeyed, however, can totally obviate the power of the techniques that have been developed to truly individualize therapy. The onus is on all clinicians to avoid falling into this trap. Though idealistically just knowing these pitfalls should make every clinician think of them and avoid them, this obviously does not occur in the real world. Consequently, it is my feeling that any request for a serum concentration sent to the clinical laboratory should be accompanied by data demonstrating that the concentration is likely to be interpretable; namely, the route of administration of the drug, its time of administra-

tion, the time of sampling, and whether or not the patient is at steady-state, should all be required on the laboratory request. If any are absent, the concentration should not be determined. I challenge Parkland Hospital to implement such a policy. Protests would be vigorous and loud, particularly among those who are the most frequent violators of these simple principles. The cost of forcing clinicians to provide such information and follow the simple principles is a small increment in time. The benefits are potentially enormous. Fewer useless serum drug concentration determinations would be performed, misinterpretation would not occur, and therefore, quality of care would improve. Not instigating such a policy seems indefensible.

Lastly, for measures of a serum drug concentration to be useful, it is important that the time of dosing and sampling be accurate. As such, the nursing service and blood drawing teams must be active partners in our attempt to appropriately use this technology. Armitstead and Nahata recently published interesting data depicted in Table 14.

TABLE 14

POTENTIAL MEDICATION ADMINISTRATION ERRORS

(Clin Pharm 2:153-156, 1983)

Method of Administration: Continuous infusion (30 min) of 100 ml by IV piggyback

Errors:
- Fluid not infused: 7.2 ± 1.2 ml (4.5-9.5)
- Dose lost: 7.2% (4.1-10.1)
- Infusion duration: 39.8 ± 20.8 min (5-110)
- Infusion started: 14.4 ± 46.9 min late (-50-200)
- Trough sampled: 9 ± 39 min (-130-90)
- Peak sampled: 44 ± 34 min (0-105)
- Peak sampling reported 6.1 ± 4.8 min later than actually drawn

These investigators monitored administration of an aminoglycoside antibiotic and the obtaining of a serum sample for measurement in a clinical laboratory. The drug was supposed to be administered as a continuous infusion over 30 minutes in 100 ml of fluid by intravenous piggyback. An average of 7 ml of fluid was not administered, and consequently, dose was inaccurate. The infusion duration, a paramter important for individualizing therapy and for making certain that the sample was not drawn during the distribution phase ranged from 5-110 minutes. The dose was started from 50 minutes early to 200 minutes late, the trough was sampled from 130 minutes too early to 90 minutes too late, and the peak was sampled up to 105 minutes late. Moreoever, the time at which it was reported that the samples were drawn was also inaccurate. All of these pieces of data would be important for interpreting any serum drug concentration. It is clear from these data that if one is to be certain of how and when the drug is administered and how and when the sample was obtained, he may have to do it himself, particularly until the ancillary personnel have been appropriately schooled (browbeaten) to recognize the importance of performing their tasks accurately. Again, these problems should be avoidable, and I challenge the nursing service and the blood drawing teams to make certain that such administration errors are avoided.

CONCLUSION

I am absolutely convinced, and I hope that I have convinced you that obtaining serum drug concentrations is not only exceedingly useful but it in fact is the only method by which we can optimize therapy with a number of drugs. In the past, such measures have been under-utilized at this hospital and many others. We now have the technology to implement

these therapeutic strategies and improve patient care. The effort must come from a variety of directions. The clinical laboratory must exercise high levels of quality control and provide concentration values in a timely fashion. The clinician must avoid the pitfalls discussed above which render interpretability impossible. And, finally, our partners in clinical care must make certain that the patient receives the drug when he is supposed to and that samples be drawn as indicated. I hope it is not too idealistic to think that collation of these efforts can occur so that we can more appropriately use the powerful drugs in our armamentarium.

I would like to dedicate this grand rounds and this efffort by our laboratory to Polavat Chennavasin. Polavat was the first postdoctoral fellow to work in my laboratory. He had a brief exposure to Clinical Pharmacology during his residency in his home country of Thailand. From this exposure, he decided that his goal was to become the first Clinical Pharmacologist in Thailand. In pursuit of that goal, he repeated his entire internship and residency in the United States so that he would have unhindered access to patient care in pursuing his Clinical Pharmacology training. He came to Dallas and worked in our group for two and one-half years after which he fulfilled his goal of becoming the first Clinical Pharmacologist in Thailand. He was one of the smartest people I ever met, but more importantly he was kind, patient, and gentle--a truly giving person. He, his wife, and six other young faculty members drowned in a tragic boating accident in mid-April of this year. All those who knew Polavat respected and loved him. He was an integral component of our first steps down this road I have presented today. In his memory, we will traverse its course.

REFERENCES

1. Anderson, A.C.; Hodges, G.R. and Barnes, W.G.: Determination of serum gentamicin sulfate levels. Ordering patterns and use as a guide to therapy. Archives of Internal Medicine 136: 785-787 (1976).

2. Anderson, E.T.; Young, L.S. and Hewitt, W.L.: Simultaneous antibiotic levels in "breakthrough" gram-negative rod bacteremia. American Journal of Medicine 61: 493-497 (1976).

3. Anderson, G.; Koup, J.; Slaughter, R.; Edwards, W.D.; Resmen, B. and Hook, E.: Evaluation of two methods for estimating theophylline clearance prior to achieving steady state. Therapeutic Drug Monitoring 3: 325-332 (1981).

4. Anonymous: IV Dosage Guidelines for Theophylline Products. FDA Drug Bulletin, (1980).

5. Anonymous: The nomogram: A more accurate dosage calculator. Drug Therapy 5: 159-163 (1975).

6. Armitstead, J.A. and Nahata, M.C.: Effect of variables associated with intermittent gentamicin infusions on pharmacokinetic predictions. Clinical Pharmacy 2: 153-156 (1983).

7. Barza, M. and Lauermann, M.: Why monitor serum levels of gentamicin? Clinical Pharmacokinetics 3: 202-215 (1978).

8. Barza, M.; Brown, R.B.; Shen, D.; Gibaldi, M. and Weinstein L.: Predictability of blood levels of gentamicin in man. Journal of Infectious Diseases 132: 165-174 (1975).

9. Beller, G.A.; Smith, T.W.; Abelmann, W.H., Haber, E. and Hood, W.B.: Digitalis intoxication. A prospective clinical study with serum level correlations. New England Journal of Medicine 284: 989-997 (1971).

10. Bennett, S.W. and Scott, A.C.: Computer-assisted customized antimicrobial dosages. American Journal of Hospital Pharmacy 37: 523-529 (1980).

11. Bernabei, R.; Perna, G.P.; Carosella, L.; DiNardo, P.; Cocchi, A.; Weisz, A.M. ad Carbonin, P.U.: Digoxin serum concentration measurement in patients with suspected digitalis-induced arrhythmias. Journal of Cardiovascular Pharmacology 2: 319-329 (1980).

12. Bollish, S.J.; Kelly, W.N.; Miller, D.E. and Timmons, R.G.: Establishing an aminoglycoside pharmacokinetic monitoring service in a community hospital. American Journal of Hospital Pharmacy 38: 73-76 (1981).

13. Bootman, J.L.; Wertheimer, A.I.; Zaske, D. and Rowland, C.: Individualizing gentamicin dosage regimens in burn patients with gram-negative septicemia: A cost-benefit analysis. Journal of Pharmaceutical Sciences 68: 267-272 (1979).

14. Buchthal, F.; Svensmark, O. and Schiller, P.J.: Clinical and electroencephalographic correlations with serum levels of diphenylhydantoin. Archives of Neurology 2: 624-630 (1960).

15. Buice, R.G.: The programmable hand-held calculator. A powerful tool in clinical pharmacokinetics. Drug Intelligence and Clinical Pharmacy 13: 328-333 (1979).

16. Chan, R.A.; Benner, E.J. and Hoeprich, P.D.: Gentamicin therapy in renal failure: A nomogram for dosage. Annals of Internal Medicine 76: 773-778 (1972).

17. Chennavasin, P. and Brater, D.C.: Aminoglycoside dosage adjustment in renal failure: A hand-held calculator program. European Journal of Clinical Pharmacology 22: 91-94 (1982).

18. Chennavasin, P. and Brater, D.C.: Nomograms for drug use in renal disease. Clinical Pharmacokinetics 6: 193-214 (1981).

19. Chow, M.S.S. and Ronfeld, R.A.: Pharmacokinetic data and drug monitoring: I. Antibiotics and antiarrhythmics. Journal of Clinical Pharmacology 15: 405-418 (1975).

20. Churchill, D.N.; McNamara, J.A.; Bowmer, M.I.; Ahmed, M. and Gault, M.H.: Predictability of serum gentamicin concentrations in renal failure. Cardiovascular Medicine 3: 1307-1310 (1978).

21. Coleman, R.W. and Hedberg, R.L.: Comparison of three methods for estimating theophylline pharmacokinetics. Clinical Pharmacy 2: 148-152 (1983).

22. Cottrell, J.J.; Pennock, B.E.; Grenvik, A. and Rogers, R.M.: Critical care computing. Journal of the American Medical Association 248: 2289-2291 (1982).

23. Cruse, K.L. and Garrett, D.G.: Gentamicin therapy in a rural community hospital. Development of a gentamicin monitoring service. Hospital Formulary 18: 276-283 (1983).

24. Cutler, G.E. and Orme, B.M.: Correlation of serum creatinine concentration and kanamycin half-life. Therapeutic implications. Journal of the American Medical Association 209: 539-542 (1969).

25. DeRepentigny, L.; Dumont, L.; LeLorier, J.; Morisset, R.; Larochelle, P. and Courchesne, Y.: Gentamicin: use of a programmable calculator to determine dosages from pharmacokinetic data for individual patients. Canadian Medical Association Journal 124: 1459-1463, 1981.

26. Duhme, D.W.; Greenblatt, D.J. and Koch-Weser, J.: Reduction of digoxin toxicity associated with measurement of serum levels. A report from the Boston Collaborative Drug Surveillance Program. Annals of Internal Medicine 80: 516-519 (1974).

27. Dvorchik, B.H. and Vesell, E.S.: Pharmacokinetic interpretation of data gathered during therapeutic drug monitoring. Clinical Chemistry 22: 868-878 (1976).

28. Elenbaas, R.M.; Payne, V.W. and Bauman, J.L.: Influence of clinical pharmacist consultations on the use of drug blood level tests. American Journal of Hospital Pharmacy 37: 61-64 (1980).

29. Fell, P.J. and Stevens, M.T.: Pharmacokinetics-uses and abuses. European Journal of Clinical Pharmacology 8: 241-248 (1975).

30. Floyd, R.A. and Taketomo R: Serum drug level usage review--a clinical pharmacy service. Drug Intelligence and Clinical Pharmacy 13: 44-45 (1979).

31. Flynn, T.W.; Pevonka, M.P.; Yost, R.L.; Weber, C.E. and Stewart, R.B.: Use of serum gentamicin levels in hospitalized patients. American Journal of Hospital Pharmacy 35: 806-808 (1978).

32. Follath, F.; Ganzinger, U. and Schuetz, E.: Reliability of anti-arrhythmic drug plasma concentration monitoring. Clinical Pharmacokinetics 8: 63-82 (1983).

33. Foster, T.S. and Bourne, D.W.A.: Use of a programmable hand-held calculator for clinical pharmacokinetics. American Journal of Hospital Pharmacy 34: 70-75 (1977).

34. Frewin, D.B.; Shaw, D.R. and Bochner, F.: Therapeutic drug monitoring: a survey of sub- and supra-therapeutic serum drug levels in a large teaching hospital. New Zealand Medical Journal 95: 774-776 (1982).

35. Galeazzi, R.L.; Benet, L.Z. and Sheiner, L.B.: Relationship between the pharmacokinetics and pharmacodynamics of procainamide. Clinical Pharmacology and Therapeutics 20: 278-289 (1976).

36. Gee, J.P. and Jim, L.K.: Program for aminoglycoside dosage calculations using an inexpensive calculator. American Journal of Hospital Pharmacy 39: 1508-1510 (1982).

37. Gibaldi, M. and Levy, G.: Pharmacokinetics in clinical practice. 1. Concepts. Journal of the American Medical Association 235: 1864-1867 (1976).

38. Gibaldi, M. and Levy, G.: Pharmacokinetics in clinical practice. 2. Applications. Journal of the American Medical Association 235: 1987-1992 (1976).

39. Goodman, E.L.; VanGelder, J.; Holmes, R.; Hull, A.R. and Sanford J.P.: Prospective comparative study of variable dosage and variable frequency regimens for administration of gentamicin. Antimicrobial Agents and Chemotherapy 8: 434-438 (1975).

40. Greenblatt, D.J. and KochWeser, J.: Clinical pharmacokinetics. New England Journal of Medicine 293: 702-705 and 964-970 (1975).

41. Greenblatt, D.J.; Bolognini, V.; Koch-Weser, J. and Harmatz, J.S.: Pharmacokinetic approach to the clinical use of lidocaine intravenously. Journal of the American Medical Association 236: 273-277 (1976).

42. Greenlaw, C.W.; Geiger, G.S. and Haug, M.T.: Use of digoxin serum assays in a nonteaching hospital. American Journal of Hospital Pharmacy 37: 1466-1470 (1980).

43. Guentert, T.W.; Upton, R.A.; Holford, N.H.G. and Riegelman, S.: Divergence in pharmacokinetic parameters of quinidine obtained by specific and nonspecific assay methods. Journal of Pharmacokinetics and Biopharmaceutics 7: 303-311 (1979).

44. Haerer A.F. and Grace, J.B.: Studies of anticonvulsant levels in epileptics. I.Serum diphenylhydantoin concentrations in a group of medically indigent outpatients. Acta Neurologica Scandinavica 45: 18-31 (1969).

45. Hendeles, L.; Bighley, L.; Richardson, R.H.; Hepler, C.D. and Carmichael J.: Frequent toxicity from IV aminophylline infusions in critically ill patients. Drug Intelligence and Clinical Pharmacy 11: 12-18 (1977).

46. Hendeles, L.; Weinberger, M. and Johnson, G.: Monitoring serum theophylline levels. Clinical Pharmacokinetics 3: 294-312 (1978).

47. Hewitt, W.L. and McHenry, M.C.: Blood level determinations of antimicrobial drugs. Some clinical considerations. Medical Clinics of North America 62: 1119-1140 (1978).

48. Hladik, W.B. and Dujovne, C.A.: One hundred digitalis-blood levels. A utilization review. European Journal of Clinical Pharmacology 15: 411-415 (1979).

49. Hull, J.H. and Sarubbi, F.A.: Gentamicin serum concentrations: Pharmacokinetic predictions. Annals of Internal Medicine 85: 183-189 (1976).

50. Ingelfinger, J.A. and Goldman, P.: The serum digitalis concentration--does it diagnose digitalis toxicity? New England Journal of Medicine 294: 867-870, 1976.

51. Jackson, E.A. and McLeod D.C.: Pharmacokinetics and dosing of antimicrobial agents in renal impairment. American Journal of Hospital Pharmacy 31: 36-52 and 137-148 (1974).

52. Jacobs, M.H.; Senior, R.M. and Kessler, G.: Clinical experience with theophylline. Relationships between dosage, serum concentration, and toxicity. Journal of the American Medical Association 235: 1983-1986 (1976).

53. Jelliffe, R.W. and Brooker, G.: A nomogram for digoxin therapy. American Journal of Medicine 57: 63-68 (1974).

54. Jelliffe, R.W.; Buell, J., and Kalaba, R.: Reduction of digitalis toxicity by computer-assisted glycoside dosage regimens. Annals of Internal Medicine 77: 891-906 (1972).

55. Jelliffe, R.W.; Schumitzky, A.; D'Argenio, D.Z. and Katz, D.: Improved M.A.P. Bayesian time-shared computer programs for adaptive control of aminoglycoside therapy. Clinical Pharmacology and Therapeutics 33: 255 (1983) (abstract).

56. Jelliffe, R.W.; Schumitzky, A.; D'Argenio, D.Z.; Katz, D. and Nicholson, W.F.: An improved M.A.P. Bayesian computer program for adaptive control of lidocaine therapy. Clinical Pharmacology and Therapeutics 33: 255 (1983) (abstract).

57. Jenne, J.W.; Wyze, E.; Rood, F.S. and MacDonald, F.M.: Pharmacokinetics of theophylline. Application to adjustment of the clinical dose of aminophylline. Clinical Pharmacology and Therapeutics 13: 349-360 (1972).

58. Johannessen, S.I.: Antiepileptic Drugs: Pharmacokinetic and clinical aspects. Therapeutic Drug Monitoring 3: 17-37 (1981).

59. Jones, W.N.; Perrier, D.; Trinca, C.E.; Hager, W.D. and Conrad, K.: Evaluation of various methods of digoxin dosing. Journal of Clinical Pharmacology 22: 543-550 (1982).

60. Jusko, W.J.; Gardner, M.J.; Mangione, A.; Schentag, J.J.; Koup, J.R. and Vance, J.W.: Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. Journal of Pharmaceutical Sciences 68: 1358-1366 (1979).

61. Jusko, W.J.; Koup, J.R.; Vance, J.W.; Schentag, J.J. and Kuritzky, P.: Intravenous theophylline therapy: Nomogram guidelines. Annals of Internal Medicine 86: 400-404 (1977).

62. Kaye, D.; Levison, M.E. and Labovitz, E.D.: The unpredictability of serum concentrations of gentamicin: Pharmacokinetics of gentamicin in patients with normal and abnormal renal function. Journal of Infectious Diseases 130: 150-154 (1974).

63. Klastersky, J.; Daneau, D.; Swings, G. and Weerts, D.: Antibacterial activity in serum and urine as a therapeutic guide in bacterial infections. Journal of Infectious Diseases 129: 187-193 (1974).

64. Klotz, U.: Pathophysiological and disease-induced changes in drug distribution volume: Pharmacokinetic implications. Clinical Pharmacokinetics 1: 204-218 (1976).

65. Koch-Weser, J.: Serum drug concentrations as therapeutic guides. New England Journal of Medicine 287: 227-231 (1972).

66. Koch-Weser, J.: Serum procainamide levels as therapeutic guides. Clinical Pharmacokinetics 2: 389-402 (1977).

67. Koch-Weser, J.: The serum level approach to individualization of drug dosage. European Journal of Clinical Pharmacology 9: 1-8 (1975).

68. Koch-Weser, J. and Klein, S.W.: Procainamide dosage schedules, plasma concentrations, and clinical effects. Journal of the American Medical Association 215: 1454-1460 (1971).

69. Koch-Weser, J.; Duhme, D.W. and Greenblatt, D.J.: Influence of serum digoxin concentration measurements on frequency of digitoxicity. Clinical Pharmacology and Therapeutics 16: 284-287 (1974).

70. Koup, J.R.; Sack, C.M.; Smith, A.L. and Gibaldi, M.: Hypothesis for the individualisation of drug dosage. Clinical Pharmacokinetics 4: 460-469 (1979).

71. Koup, J.R.; Schentag, J.J.; Vance, J.W.; Kuritzky, P.M.; Pyszczynski, D.R. and Jusko, W.J.: System for clinical pharmacokinetic monitoring of theophylline therapy. American Journal of Hospital Pharmacy 33: 949-956 (1976).

72. Kutt, H. and Penry, J.K.: Usefulness of blood levels of antiepileptic drugs. Archives of Neurology 31: 283-288 (1974).

73. Kutt, H.; Winters, W.; Kokenge, R. and McDowell, F.: Diphenylhydantoin metabolism, blood levels, and toxicity. Archives of Neurology 11: 642-648 (1964).

74. Lehmann, C.R. and Leonard R.G.: Effect of theophylline pharmacokinetic monitoring service on cost and quality of care. American Journal of Hospital Pharmacy 39: 1656-1662 (1982).

75. Lenert, L.; Platzer, R.; Peck, C.; Galeazzi, R.; Dayan, E.; Baker, J.; Smith, L. and Ezra, D.: Bayesian pharmacokinetic forecasting as a research tool. Clinical Pharmacology and Therapeutics 33: 201 (1983) (abstract).

76. Lesar, T.S.; Rotschafer, J.C.; Strand, L.M.; Solem, L.D. and Zaske, D.E.: Gentamicin dosing errors with four commonly used nomograms. Journal of the American Medical Association 248: 1190-1193 (1982).

77. Lima, J.J.; Conti, D.R.; Goldfarb, A.L.; Golden, L.H. and Jusko, W.J.: Pharmacokinetic approach to intravenous procainamide therapy. European Journal of Clinical Pharmacology 13: 303-308 (1978).

78. Loirat, P.; Rohan, J.; Baillet, A.; Beaufils, F.; David, R. and Chapman, A.: Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. New England Journal of Medicine 299: 915-919 (1978).

79. Loughnan, P.M.; Sitar, D.S.; Ogilvie, R.I. and Neims, A.H.: The two-compartment open-system kinetic model: A review of its clinical implications and applications. Journal of Pediatrics 88: 869-873 (1976).

80. Ludden, T.M.; Allen, J.P.; Valutsky, W.A.; Vicuna, A.V.; Nappi, J.M.; Hoffman, S.F.; Wallace, J.E.; Lalka, D. and McNay, J.L.: Individualization of phenytoin dosage regimens. Clinical Pharmacology and Therapeutics 21: 287-292 (1977).

81. Lund, L.: Anticonvulsant effect of diphenylhydantoin relative to plasma levels. Prospective three year study in ambulant patients with generalized epileptic seizures. Archives of Neurology 31: 289-294 (1974).

82. Madsen, B.W.; Tarala, R.A. and Paterson, J.W.: A hand-held calculator program for individualized dosage adjustment of intravenous theophylline in acute asthma. European Journal of Clinical Pharmacology 17: 393-399 (1980).

83. Mawer, G.E.; Ahmad, R.; Dobbs, S.M.; McGough, J.G.; Lucas, S.B. and Tooth, J.A.: Prescribing aids for gentamicin. British Journal of Clinical Pharmacology 1: 45-50 (1974).

84. McCormick, W.; Ingelfinger, J.A.; Isakson, G. and Goldman, P.: Errors in measuring drug concentrations. New England Journal of Medicine 299: 1118-1121 (1978).

85. McGory, R.W. and Matzke, G.R.: Evaluation of a single-point method for predicting theophylline dosage. Clinical Pharmacy 1: 441-446 (1982).

86. McHenry, M.C.; Gavan, T.L.; Gifford, R.W.; Geurkink, N.A.; VanOmmen, R.A.; Town, M.A. and Wagner, J.G.: Gentamicin dosages for renal insufficiency. Adjustments based on endogenous creatinine clearance and serum creatinine concentration. Annals of Internal Medicine 74: 192-197, 1971.

87. Mitenko, P.A. and Ogilvie, R.I.: Rapidly achieved plasma concentration plateaus, with observations on theophylline kinetics. Clinical Pharmacology and Therapeutics 13: 329-335 (1972).

88. Mitenko, P.A. and Ogilvie, R.I.: Rational intravenous doses of theophylline. New England Journal of Medicine 289: 600-603 (1973).

89. Mullen, P.W.: Optimal phenytoin therapy: A new technique for individualizing dosage. Clinical Pharmacology and Therapeutics 23: 228-232 (1978).

90. Mungall, D.; Bancroft, W. and Marshall, J.: Computer-assisted oral and intravenous theophylline therapy. Computers and Biomedical Research 15: 18-28 (1982).

91. Ng, P.K.: Determining aminoglycoside dosage and blood levels using a programmable calculator. American Journal of Hospital Pharmacy 37: 225-231 (1980).

92. Ng, P.K.: Individualizing phenytoin dosage regimens using a programmable calculator. American Journal of Hospital Pharmacy 37: 529-533 (1980).

93. Nicholson, P.W.; Dobbs, S.M. and Rodgers, E.M.: Ideal sampling time for drug assays. British Journal of Clinical Pharmacology 9: 467-470 (1980).

94. Noone, P.; Beale, D.F.; Pollock, S.S.; Perera, M.R.; Amirak, I.D.; Fernando, O.N. and Moorhead, J.F.: Monitoring aminoglycoside use in patients with severely impaired renal function. British Medical Journal 2: 470-473 (1978).

95. Noone, P.; Parsons, T.M.C.; Pattison, J.R.; Slack, R.C.B.; Garfield-Davies, D. and Hughes, K.: Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. British Medical Journal 1: 477-481 (1974).

96. Pancorbo, S.; Davies, S. and Raymond, J.L.: Use of a pharmacokinetic method for establishing doses of aminophylline to treat acute bronchospasm. American Journal of Hospital Pharmacy 38: 851-856 (1981).

97. Pechere, J.-C. and Dugal, R.: Clinical pharmacokinetics of aminoglycoside antibiotics. Clinical Pharmacokinetics 4: 170-199 (1979).

98. Peck, C.; Lenert, L. and Nichols, A.: A prototype bayesian pharmacodynamic microcomputer program for optimizing drug therapy. Clinical Pharmacology and Therapeutics 33: 201 (1983) (abstract).

99. Pfeifer, H.J.; Greenblatt, D.J. and Koch-Weser, J.: Clinical use and toxicity of intravenous lidocaine. A report from the Boston collaborative drug surveillance program. American Heart Journal 92: 168-173 (1976).

100. Platt, D.R.; Matthews, S.J.; Sevka, M.J.; Comer, J.B.; Quintiliani, R.; Cunha, B.A.; Nightingale, C.H. and Chow, M.S.S.: Comparison of four methods of predicting serum gentamicin concentrations in adult patients with impaired renal function. Clinical Pharmacy 1: 361-365 (1982).

101. Powell, J.R.; Vozeh, S.; Hopewell, P.; Costello, J.; Sheiner, L.B. and Riegelman, S.: Theophylline disposition in acutely ill hospitalized patients. The effect of smoking, heart failure, severe airway obstruction, and pneumonia. American Review of Respiratory Disease 118: 229-238 (1978).

102. Reymann, M.T.; Bradac, J.A.; Cobbs, C.G. and Dismukes, W.E.: Correlation of aminoglycoside dosages with serum concentrations during therapy of serious gram-negative bacillary disease. Antimicrobial Agents and Chemotherapy 16: 353-361 (1979).

103. Rich, D.S.; Mahoney, C.D.; Jeffrey, L.P. and Pezzullo, J.C.: Evaluation of a computerized digoxin pharmacokinetic consultation service. Hospital Pharmacy 16: 23-27 (1981).

104. Richens, A. and Dunlop, A.: Phenytoin dosage nomogram. Lancet 2: 1305-1306 (1975).

105. Richens, A. and Warrington, S.: When should plasma drug levels be monitored? Drugs 17: 488-500 (1979).

106. Sarubbi, F.A. and Hull, J.H.: Amikacin serum concentrations: Prediction of levels and dosage guidelines. Annals of Internal Medicine 89: 612-618 (1978).

107. Sawchuk, R.J.; Zaske, D.E.; Cipolle, R.J.; Wargin, W.A. and Strate, R.G.: Kinetic model for gentamicin dosing with the use of individual patient parameters. Clinical Pharmacology and Therapeutics 21: 362-369 (1977).

108. Shapiro, W.: Correlative studies of serum digitalis levels and the arrhythmias of digitalis intoxication. American Journal of Cardiology 41: 852-859 (1978).

109. Sheiner, L.B.: The use of serum concentrations of digitalis for quantitative therapeutic decisions. Cardiovascular Drug Therapy, Cardiovascular Clinic (K.L. Melmon, editor), 6: 141-152 (1974).

110. Sheiner, L.B. and Beal, S.L.: Bayesian individualization of pharmacokinetics: Simple implementation and comparison with non-bayesian methods. Journal of Pharmaceutical Sciences 71: 1344-1348 (1982).

111. Sheiner, L.B.; Beal, S.; Rosenberg, B. and Marathe, V.V.: Forecasting individual pharmacokinetics. Clinical Pharmacology and Therapeutics 26: 295-305 (1979).

112. Sheiner, L.B.; Halkin, H.; Peck, C.; Rosenberg, B. and Melmon, K.L.: Improved computer-assisted digoxin therapy. A method using feedback of measured serum digoxin concentrations. Annals of Internal Medicine 82: 619-627 (1975).

113. Sheiner, L.B.; Melmon, K.L., and Rosenberg, B.: Instructional goals for physicians in the use of blood level data-and the contribution of computers. Clinical Pharmacology and Therapeutics 16: 260-271 (1974).

114. Sketris, I.; Lesar, T.; Zaske, D.E. and Cipolle, R.J.: Effect of obesity on gentamicin pharmacokinetics. Journal of Clinical Pharmacology 21: 288-293 (1981).

115. Slattery, J.T.; Gibaldi, M. and Koup, J.R.: Pharmacokinetic Concepts: Prediction of maintenance dose required to attain a desired drug concentration at steady-state from a single determination of concentration after an initial dose. Clinical Pharmacokinetics 5: 377-385 (1980).

116. Slaughter, R.L.; Schneider, P.J. and Visconti, J.A.: Appropriateness of the use of serum digoxin and digitoxin assays. American Journal of Hospital Pharmacy 35: 1376-1379 (1978).

117. Smith, T.W.: Digitalis Toxicity: Epidemiology and clinical use of serum concentration measurements. American Journal of Medicine 58: 470-476 (1975).

118. Smith, T.W. and Haber, E.: Digoxin intoxication. The relationship of clinical presentation to serum digoxin concentration. Journal of Clinical Investigation 49: 2377-2386 (1970).

119. Solem, L.D.; Zaske, D. and Strate, R.G.: Ecthyma gangrenosum. Survival with individualized antibiotic therapy. Archives of Surgery 114: 580-583 (1979).

120. Stargel, W.W.; Shand, D.G.; Routledge, P.A.; Barchowsky, A. and Wagner, G.S.: Clinical comparison of rapid infusion and multiple injection methods for lidocaine loading. American Heart Journal 102: 872-876 (1981).

121. Vozeh, S.; Berger, M.; Ritz, R. and Follath, F.: Accurate prediction of lidocaine individual dosage requirements. Clinical Pharmacology and Therapeutics 33: 212 (1983) (abstract).

122. Vozeh, S.; Kewitz, G.; Wenk, M. and Follath, F.: Rapid prediction of steady-state serum theophylline concentration in patients treated with intravenous aminophylline. European Journal of Clinical Pharmacology 18: 473-477 (1980).

123. Vozeh, S.; Muir, K.T.; Sheiner, L.B. and Follath, F.: Predicting individual phenytoin dosage. Journal of Pharmacokinetics and Biopharmaceutics 9: 131-146 (1981).

124. Weinberger, M.W.; Matthay, R.A.; Ginchansky, E.J.; Chidsey, C.A. and Petty, T.L.: Intravenous aminophylline dosage. Use of serum theophylline measurement for guidance. Journal of the American Medical Association 235: 2110-2113 (1976).

125. Weintraub, M.: Interpretation of the serum digoxin concentration. Clinical Pharmacokinetics 2:205-219 (1977).

126. Welling, P.G., Craig, W.A. and Kunin, C.M.: Prediction of drug dosage in patients with renal failure using data derived from normal subjects. Clinical Pharmacology and Therapeutics 18: 45-52 (1975).

127. Wilson, J.T. and Wilkinson, G.R.: Delivery of anticonvulsant drug therapy in epileptic patients assessed by plasma level analyses. Neurology 24: 614-623 (1974).

128. Wright, N.: The clinical relevance of pharmacokinetics. Journal of Antimicrobial Chemotherapy 10: 2-4 (1982).

129. Yee, G.C. and Evans, W.E.: Reappraisal of guidelines for pharmacokinetic monitoring of aminoglycosides. Pharmacotherapy 1: 55-75 (1981).

130. Zaske, D.E.; Cipolle, R.J. and Strate, R.J.: Gentamicin dosage requirements: Wide interpatient variations in 242 surgery patients with normal renal function. Surgery 87: 164-169 (1980).

131. Zaske, D.E.; Irvine, P.; Strand, L.M.; Strate, R.G.; Cipolle, R.J. and Rotschafer, J.: Wide interpatient variations in gentamicin dose requirements for geriatric patients. Journal of the American Medical Association 248: 3122-3126 (1982).

132. Zaske, D.E.; Sawchuk, R.J.; Gerding, D.N. and Strate, R.G.: Increased dosage requirements of gentamicin in burn patients. Journal of Trauma 16: 824-828 (1976).